REARRANGEMENTS OF STEROIDS OF UNNATURAL CONFIGURATION

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CONTENTS

ABSTRACT

Lithium-ammonia reduction of 10α-cholest-5,7-dien-3β-ol (5h) gave the 5α-Δ^7-olefins (5β:5α; 63:15). Perbenzoic acid oxidation of the diene (5h) gave 5,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c, 60%); 5β,10α-cholest-7-en-3β,5,6α-triol (70d, 25%); and 3β,6β-oxido-5α,10α-cholest-7-en-5-ol (71b, 12%). The ether (71b) is thought to arise via 5α,6α-epoxide (72d) which was not isolated.

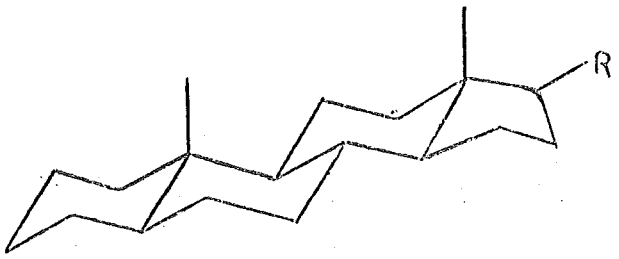
Reduction of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f) with sodium borohydride-pyridine afforded the Δ^7-6α-alcohol (70d; 14%). Lithium-ammonia reduction of enone (70f) gave 3β,5-dihydroxy- and 3β-hydroxy-5β,8α,10α-cholestan-6-one (84b, 32%; 84a, 4%), 5α,10α-cholestane-3β,6α-diol (85a, 14%), 5β,8α,10α-cholestane-3β,6β-diol (84e, 30%), and 5β,10α-cholest-7-ene-3β,5,6β-triol (70h , 3%).

Epoxidation of 5β,10α-cholest-7-en-3β-ol (65c) gave the 7α,8α-epoxide (100) which under acidic conditions produced the 7-ketone (104). Lithium-ethylamine reduction of epoxide (100) gave the 5β,8α,10α: 7α-alcohol (112b; 50%) and the 5β,8α,10α:8-alcohol (113b, 12%).

Base and additive shift values for angular methyl groups are estimated for the 5β, 8α, 10α and 5α, 10α-series and the dependence of these shifts on skeletal structure is discussed.

SKELETAL ISOMERS IN THE STEROIDS

The steroid skeleton (1) contains seven asymmetric centres and therefore has one hundred and twenty eight possible stereoisomeric forms. The commonest of these is the naturally occuring '5α, 8β, 9α, 10β, 13β, 14α, 17β' isomer shown in Fig. 1. Steroids with the alternate configuration at C(5) are also



-Fig. 1-

common - coprostan-3β-ol (5β-cholestan-3β-ol;2) is a naturally occuring example. Indeed they are so abundant that IUPAC nomenclature[1] of steroids requires the C(5) configuration to be specified; all other centres are assumed to be as in Fig. 1 unless otherwise indicated. 14β-Steroids also occur naturally - toad poisons and cardiac aglucones (e.g. digitoxigenin (3)) are examples of this group. The term 'natural' is applied to steroids with the alternating 13β, 14α, 8β, 9α, 10β backbone and the 17β-substituent; 'unnatural' steroids are those with any other skeletal form.

The unnatural steroids represent an incidental chapter

in the vast steroid literature. For a considerable period few examples were known and these largely only as by-products of total synthetic routes to natural steroids. However in 1948 Ehrenstein[2] reported 19-Nor-14β, 17α-progesterone (4a) which was more active[3] than its natural analogue, progesterone (4b). This result prompted work on synthetic routes to 14β, 17α-progesterone (4c)[4, 5] and 19-nor-steroids[4, 6, 7]. Later discoveries of pharmacologically active compounds with 9β, 10α[8, 9, 10, 11] and 8α[12, 13, 14]-configurations gave further impetus to work on 'unnatural' steroids.

SYNTHETIC ROUTES TO UNNATURAL STEROIDS

(1) Photolytic and pyrolytic route to C(9), C(10) isomers.

Early work on the photolysis of steroidal $\Delta^{5,7}$-dienes was stimulated by the discovery of antirachitic activity in the irradiation products of ergosterol (5a) and cholesterol (6a). Windaus et al[15] reported a potent crystalline product, "vitamin D_1", from ergosterol (5a).* They later reported a more active product, vitamin D_2 (7a)[16] and determined that "Vitamin D_1", was a 1:1 complex of vitamin D_2 (7a) and a non-active component, lumisterol** (5b)[1]

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*ergosta-5, 7, 22-trien-3β-ol

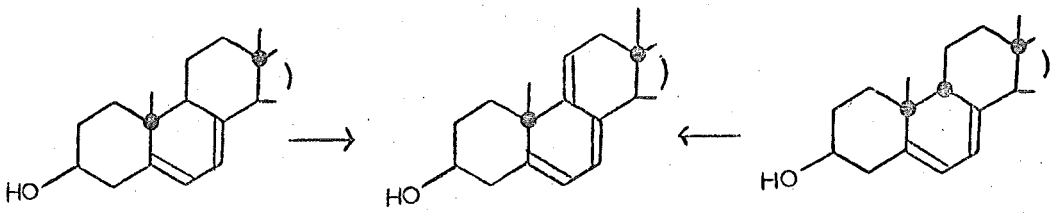
**9β, 10α-ergosta-5, 7, 22-trien-3β-ol

Simultaneously a British group reported the same results[18, 19] but named vitamin D_2, calciferol. Antirachitic activity was also induced in cholesterol (6a) by irradiation although it was later found that the potency of the product depended on the extent of a diene impurity in the cholesterol[20] (6a). Windaus et al.[21] converted 7-dehydro-cholesterol (5f) to a product as potent as natural vitamin D concentrates, plus a non-active steroidal component, 9β, 10α-cholesta-5, 7-dien-3β-ol (5g).

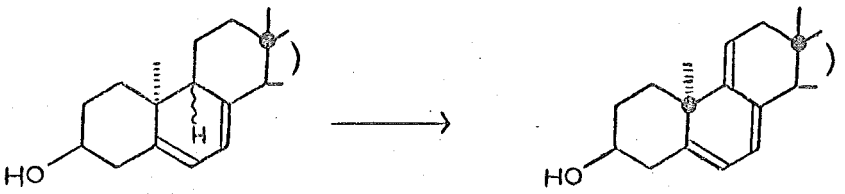
The irradiation of ergosterol yields four well defined photoisomers as well as others as yet unidentified[22]. The currently accepted scheme for this photoisomerization was established by Velluz et al[23]. The yield of lumisterol (5b) is maximized by irradiation with light of wavelength greater than 280mμ[24]. Pyrolysis of vitamin D_2 (7a) gave two more steroidal isomers, pyrocalciferol (5c)[25, 26] and isopyrocalciferol (5d)[26]. Similarly pyrolysis of vitamin D_3 gives isopyro- (5i) and pyro- (5h) isomers.

Lumisterol (5b), pyrocalciferol (5c) and isopyrocalciferol (5d) were rigorously established to be stereoisomers of the natural (i.e. 9α, 10β) diene, ergosterol (5a), differing only in the configurations about the C-9, C-10 bond.[27] Dehydrogenation

to the $\Delta^{5,7,9(11),22}$-tetraenes (8a) and 8(b), (Fig. 2), established isopyrocalciferol (5d) as the 9β, 10β-isomer and showed lumisterol (5b) and pyrocalciferol (5c) to be 10α-steroids isomeric at C(9)[28]. Similar work was reported in the D_3 series.[29]



ergosterol (5a) (8a) isopyrocalciferol (5d)



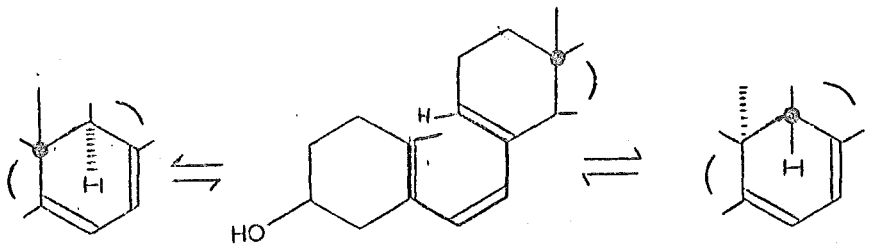
pyrocalciferol and lumisterol (5b, 5c) (8b)

-Fig. 2-

Pyrocalciferol (5c) and lumisterol (5b) were assigned as the 9β, 10α and 9α, 10α isomers on indirect evidence.[30] However Jones et al[31] degraded both lumisterol (5b) and isopyrocalciferol (5d) to des-A-9β, 10β-ergost-22-en-5-one (9) by a procedure

which leaves the C(9) stereochemistry unchanged. This established lumisterol (5b) as having the 9β,10α-structure and thus, by elimination, pyrocalciferol (5c) has the 9α, 10α-configuration. This group undertook the first systematic study of the C(9), C(10) isomers of ergosterol (5a)[32]. Since structural certainty had now been established for this series of compounds these authors rationalized the nomenclature by dropping the pyro- and isopyro- names; however they retained the name lumistane for 9β, 10α-ergostane and the trivial names ergosterol and lumisterol for the dien-ols (5a, 5b). This nomenclature has since been superseded by the IUPAC system[1] which from this point in the thesis will generally be used.

The formation of isomeric dienes by photolysis and pyrolysis, as described above, can be rationalized in terms of the concepts of orbital symmetry.[33] The interconversion of previtamin D_2(10) with 9β, 10α-ergosta-5, 7, 22-trien-3β-ol (5b) and ergosta-5, 7, 22-trien-3β-ol (5a) is an example of a hexatriene-cyclohexadiene equilibrium via the photolytically allowed conrotatory mode,[33a] (Fig. 3).

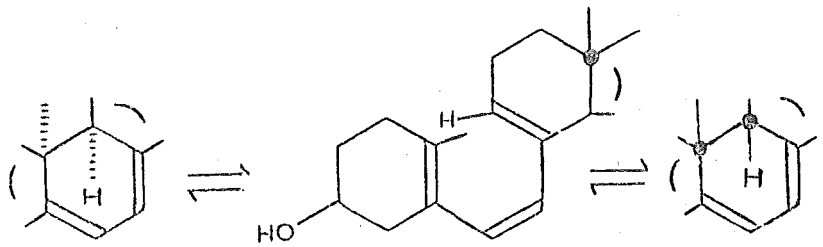


(5a) Previtamin D_2(10) (5b)

-Fig. 3-

Similarly the C(9), C(10) <u>syn</u> isomers (5c, 5d) are formed by a disrotatory closure of previtamin D_2(10), a process which is symmetry allowed under thermal conditions,[33a] (Fig. 4).

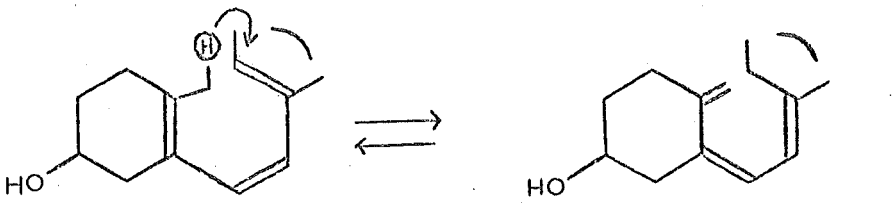
(5c) (10) (5d)



-Fig. 4-

Previtamin D_2(10) is the initial irradiation product of ergosta-5, 7, 22-trien-3β-ol (5a) and it is in thermal equilibrium with the vitamin (7a) by a 1, 7-antarafacial hydrogen shift,[33b, 23] (Fig. 5).

Previtamin D_2(10) Vitamin D_2(7a)



-Fig. 5-

In the present work the pyrolysis of vitamin D_3(7b) to 10α- and 9β-cholest-5, 7-dien-3β-ol (5h, 5i) was used as an entry to the C(9)-C(10)-syn isomers in the D_3 series. Although the full structural proof has not been established in this series the configurations follow by analogy with the D_2 series. In particular the NMR data for the dienes (5h, 5i) was consistent with data published for the D_2 series.[34]

(2) Other Chemical Routes to Unnatural Isomers

(a) 10α Isomers

Uskokovic et al[35] have converted 11α-mesyloxy-progesterone (11) into 10α- and 9β, 10α-* pregnane derivatives by reactions involving a degradation-condensation procedure. The natural steroid (11) was degraded in two steps (6%) to des-A-pregn-9(10)-en-5,20-dione (12a). Condensation of this dione (12a) with methyl vinyl ketone gave 5-hydroxy-5α,

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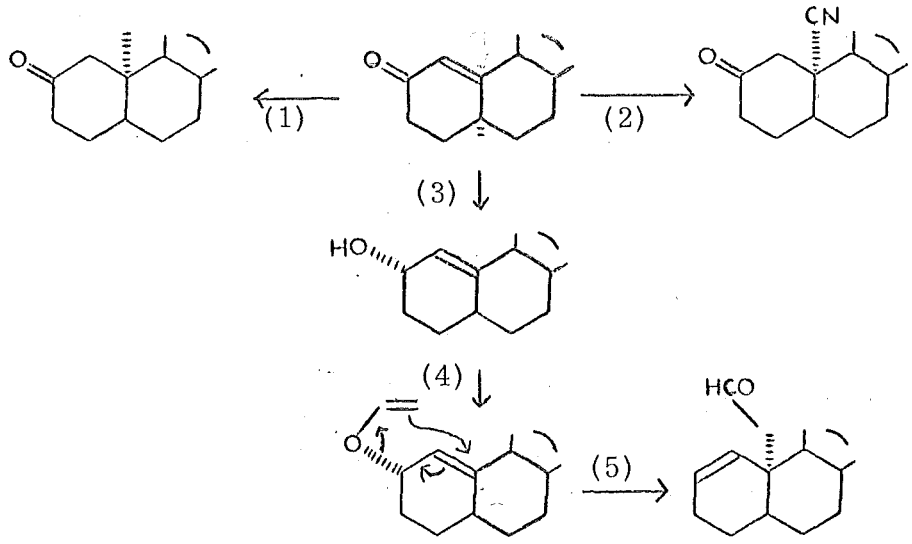
*retro-isomer

10α-pregn-9(11)-ene-3, 20-dione (13). Lithium-ammonia reduction of dione (12a) followed by in. situ. condensation with methyl vinyl ketone gave 5-hydroxy-5α, 10α-pregnane-3, 17-dione (14a). Hydrogenation of dione (12a) gave mainly the 9β-saturated derivative and this was condensed to form the 9β, 10αpregnane-derivative (14b). Cholesterol (6a) has been converted in an analogous manner[36], via des-A-cholest-9(10)-en-5-one (12b) to 10α-cholesterol (6b) in an overall yield of only 6.4%. Sondheimer et al[37] degraded testosterone (15a), in an eleven step sequence, to the des-A-ester (16) which on condensation with methyl vinyl ketone gave the esters (17a, 17b). Reduction of the ester function and dehydration of the 5α-hydroxyl leads to 19-hydroxy-10α-testosterone (15b). This was the first reported 10α-hormone analogue, however the synthetic route was tedious, gave a low yield of product (ca 1%) and has been superseded by other methods[38, 39, 49, 41].

Fishman[39, 40, 42, 43] prepared a variety of 10α-steroids from Δ^1-2-ketones by the general methods outlined in Fig. 6.



(1) MeMgX; Cu salts. (2) KCN, NH_4Cl (3) $Li(Bu^tO)_3H$

(4) R-O-CH=CH_2 (5) decalin, 195°C.

-Fig. 6-

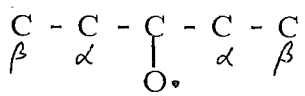
The main feature of this work was the introduction of the 10α-CN and 10α-(CH_2CHO) functions providing a convenient route to a variety of C-19 substituted 10α-steroids, e.g. 19-hydroxy-10α-testosterone (15b).

Steroids having the 10α-configuration have also been formed by Simmons-Smith methylation of $\Delta^{5(10)}$-steroids.[38] Methylation of androst-5(10)-ene-3β, 6α, 17β-triol 3-tetrahydropyranyl ether (18) gave the 5α, 10α-methano derivative (19a) which on treatment with hydrochloric acid produced

19-chloro-10α-androst-5-ene-3β, 17β-diol (20). The stereospecificity of the Simmons-Smith methylation with respect to allylic hydroxyl functions has been well established with studies on cyclohexen-2-ol derivatives.[38A] 5α, 10α-Methano-androstane-3α, 17β-diol (19b) is converted by butoxide in reluxing dimethyl sulphoxide to 10α-testosterone (15c) and the Δ^5-isomer (21).

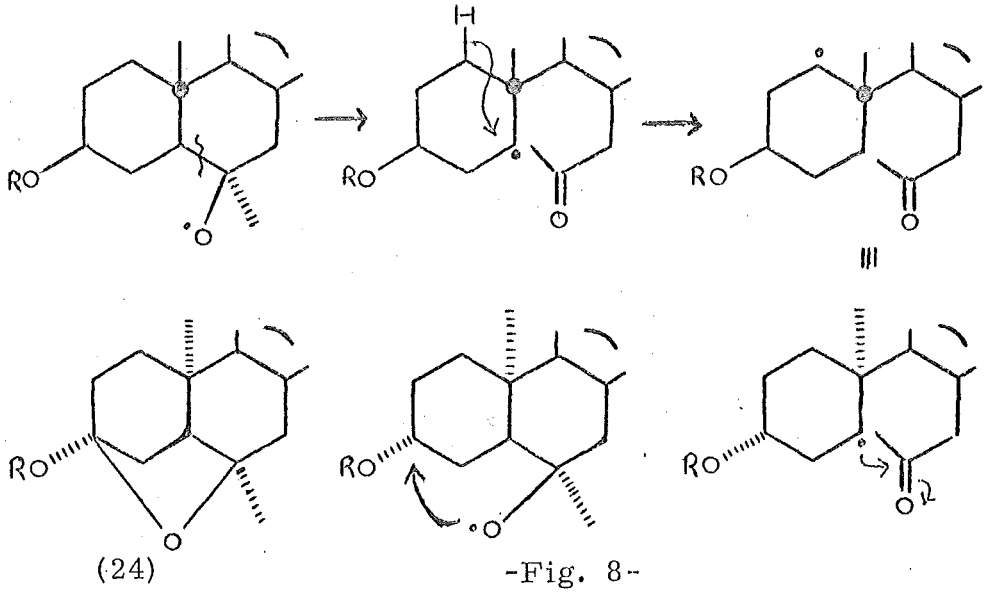
Saucy et al[44] have reported the microbiological hydroxylation at C(11) of 9β, 10α-steroids. Treatment of the corresponding 11-oxo-derivatives with acid or base resulted in equilibration at C(9). In this way 10α-cortisone (22a), 11-oxo-10α-progesterone (22b) and 10α-androst-4-en-3, 11, 17-trione (22c) were prepared.

Oxy-radicals have been found to epimerize at the α and/or β carbon atoms[45] (Fig. 7) and treatment of 6α-methyl-



-Fig. 7-

5α-pregnane -3β, 6β, 20β-triol 3, 20-diacetate (23) with lead tetra-acetate in refluxing cyclohexane produced 3β, 6β-oxido-6α-methyl-5α, 10α-pregnane-3α, 20β-diol diacetate (24, 20%)[46]. Inversion of configuration at C(10) is proposed to occur by the following mechanism[46], (Fig. 8).



-Fig. 8-

Hydrolysis of the oxido-derivative (24) provides access to a variety of 6α-methyl-10α-pregnane derivatives;[46] e.g. (25).

The 10α-configuration has also been produced by photolysis of ring A-enones and -dienones. Wenger et al[47,48] converted 3-oxo-androsta-1,4-dien-17β-yl acetate (26) into a variety of 17-oxygenated-10α-androstane derivatives including 10α-testosterone (15c). Photolysis of the dienone (26), in dioxan with light of wave length 254mμ, produces the Δ^3-1β,5β cyclo-derivative (27, 62%) which is readily hydrogenated to 1β,5—cyclo-2-oxo-5β,10α-androstan-17β-yl acetate (28a). Treatment of the latter compound (28a) with boron-trifluoride in acetic anhydride gave 5ξ,10α-androst-1-ene-2,5,17β-triol triacetate (29). The photolysis of the dienone (26)

gives a number of isomers depending on the solvent used and the 10α-cyclo derivative (27) readily photolyses to some of these isomers. However a satisfactory yield is obtained under the conditions quoted above.[47,48] Photolysis of cholest-4-en-3-one (4d) gave 1β,5β-cyclo-10α-cholestan-2-one (28b, 25%) which is converted to 5α,10α-cholestane derivatives upon treatment with acid.[49]

Hydrogenolysis of estrone (30a) over ruthenium oxide at elevated temperature and pressure gave 5α,10α-estrane-3β,17β-diol (31a; 85%)[50]. Torgov[51a] and Smith[51b] have reported the total synthesis of 19-Nor-10α-testosterone. (15d).

(b) 9β Steroids

The 9β-stereochemistry can be introduced via internal rearrangements of 9α, 11α-epoxy derivatives. Epoxidation of the readily available $\Delta^{7,9(11)}$ dienes (32) was reported to give the Δ^{7}-9α, 11α-epoxy-derivatives (33)[52] which on treatment with boron-trifluoride gave $\Delta^{8(9)}$-11-ketones (34)[53]. However a reinvestigation of these rearrangements revealed that the initial products were Δ^{7}-9β-11-ketones (35a) which isomerise to the $\Delta^{8(9)}$-isomers (34) upon treatment with acid or base[54]. Hydrogenation of the Δ^{7}-9β-11-oxo derivatives (35a) gave 9β-11-ketones (36a)[54]. Base treatment of the 9β-

11-ketones (35a, 36a) gave the more stable natural isomers (35b, 36b)[54]. ApSimon et al[55] report the boron trifluoride rearrangement of 9α, 11α-epoxy-androst-4-ene-3, 17-dione (37) to 9β-methyl-11α-hydroxy-estrone (38, 14%), 11α-hydroxy-9β-androst-4, 8(14)-diene-3, 17-dione (39, 26%) and 9β-androst-4-ene-3, 11, 17-trione (40, 4%).

9β-Estrone methyl ether (30b) has been prepared by total synthesis[56, 57]. Birch reduction of this ether gave 9β-estr-5(10)-ene-3, 17-dione (41a). Birch and Subba Rao[58] prepare 9β-testosterone (15e) via addition of a carbene to the 5(10) bond of the olefin (41a). However the carbene addition was not stereospecific and 9β, 10α-testosterone (15f) was also isolated.

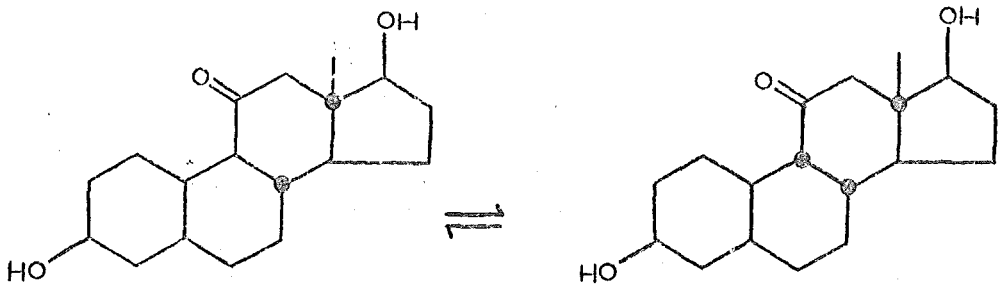
The hydrogenation of 17β-hydroxy-estra-4, 9(10)-dien-3-one (42) has been reported to give 19-Nor-9β-testosterone (15g) and 19-Nor-10α-testosterone (15h)[59]. Vigorous acid or base treatment of the 10α-isomer (15h) produces the 9β, 10α-isomer (15i).

(c) 9β, 10α-Steroids ("Retro-")

Crabbé et al[60, 61] report the preparation of 19-Nor-9β, 10α-steroids from $\Delta^{9(11)}$-A-aromatic derivatives (43). Hydroboration and oxidation of the 9(11)-olefinic bond affords the 9α, 11α-hydroxy-derivatives which on oxidation to the

11-ketones followed by base treatment gave the 9β-A-aromatic-11-ketones (44a). Birch reduction of the 3-methyl-ethers (44b) followed by acid treatment gave 19-Nor-9β, 10α-Δ^4-3-ketones (45). This reaction is analogous to that reported[62,63] for the conversion of estrone methyl ether (30c) to 19-nor-testosterone (15j). Epimerization at C-9 of A-aromatic-11-oxo-steroids have also been reported by Bailey[64] and Cashi[65].

Hydrogenation of 11α-hydroxy-estradiol (46) over ruthenium oxide produced 5α, 10α-estrane-3β, 11α, 17β-triol (47)[66]. Treatment of the 11-oxo derivative (48a) with base afforded the 9β, 10α-isomer (48b)[66]. (Fig. 9).



66% 33%

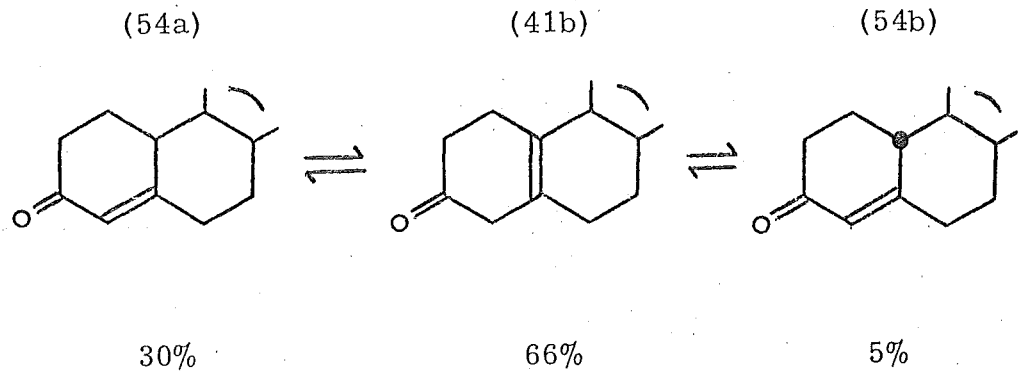
-Fig. 9-

Total syntheses have been reported for 19-nor-9β,10α-[7,67,68] and 9β, 10α-steroids[69,70,71].

(d) 8α-Steroids

19-Nor-8α-steroids have been prepared by reduction of naturally occuring compounds with an aromatic ring A and unsaturation in ring B. The readily available $\Delta^{7,9(11)}$ diene system can be converted by epoxidation and rearrangement to a $\Delta^{8(9)}$ structure; epimerization and reduction then give the 8ξ, 14ξ isomeric series. 8α-methyl steroids can be prepared by Simmons-Smith methylation of Δ^{7}-6-ols.

Hydrogenation of equilenin (49) produces estra-5(10), 6, 8(9)-trien-3β, 17β-diol(50, 50%) and 8α-estradiol (51a, 24%) [12,72,73]. The latter is also formed by hydrogenation of equilin (52)[74]. Hydrogenation of estra-1, 3, 5(10), 8(9), 14(15)-pentaen-17-one-3-methyl ether (53) gave 8α-estrone 3-methyl ether (30d)[75,76]. Birch reduction of the 3-methyl ethers of 8α-estrone (30d)[75,76] and 8α-estradiol (51b) gave the corresponding $\Delta^{5(10)}$-ene-3 ketones (41b, 41c). Treatment of 8α-estr-5(10)-ene-3, 17-dione (41b) with methanolic hydrochloric acid gave the following equilibrium[56,57] (Fig. 10).



-Fig. 10-

The Δ^4-3-ketones (54a, b) were converted to the A/B cis-(55a, b) and A/B trans-(55c, 55d) saturated derivatives by hydrogenation and lithium-ammonia reduction respectively[75,76]. In this manner the four 5ξ, 10ς, 8α-estrane skeletons can be prepared.

Djerassi et al[77,78] have prepared (25S)-5β, 8ξ, 14ξ-spirostan-11-one derivatives (56) from the readily available (25S)-5β-spirosta-7, 9(11)-diene (57). Epoxidation of the $\Delta^{7,9(11)}$-diene (57) gave the Δ^7-9α,11κ-epoxide (58) which rearranged with boron trifluoride to the $\Delta^{8(9)}$-11-

ketone* (59a). Base treatment of the latter compound effects epimerization at C(14). The 14ε, 8 (9)-en-11-ketones (59a, b) are reduced by hydrogenation and lithium-ammonia to the C(8), C(14)-syn-(56a, b) and anti-(56c, d) compounds respectively. 11-oxo-(25S)-5β, 8α-spirostan-3β-ylpropionate (56a) has been converted to 8α-progesterone (60)[13a, 13b, 79] and 8α-testosterone (15e)[14, 13a] both of which exhibit physiological activity. Total syntheses of 19-Nor-8α, 10α-testosterone (15k)[67, 72], 8α-estrone (30e)[80] and 8α-testosterone (15ℓ)[81] have been reported.

Dauben and Fullerton[82] have prepared the 6α-hydroxy-8α-methyl derivatives (61) in the cholestane and 17β-oxygenated androstane series. The sterespecific introduction of the 8α-methyl group is achieved by Simmons-Smith methylation** of the "7-en-6-ols"(62), followed by lithium-ammonia reduction of the resultant 7α, 8α-methano derivatives (63).

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*As noted previously (P.12) in the ergostane, cholestane and androstane series the Δ^7-9β-ketones are intermediates in the reaction giving access to 9β-steroids.

**Ref. P.10 this thesis.

They obtained a 5% yield of the 8α-methyl derivative (61a) from androst-5-ene-3β, 17β-diol diacetate (6c) and an 11% yield of (61b) from cholesta-5, 7-dien-3β-yl acetate (5j).

GENERAL

Johnson et al[57] have reported total syntheses of seven of the eight possible racemic forms of estrone. Westerhof et al[83] prepared 9β-ergosta-5, 7, 22-trien-3β-ol (5d) pyrolytically (Ref. Pp.2-7) and converted it to 9β-progesterone (60b) and 9β-testosterone (15e) using a sequence based on work in the 'natural' analogues[84]. They similarly prepared 9β, 10α-(retro)-[9] and 8α, 10α-[85] derivatives in these series. These authors also report the photolysis of 3β-hydroxy-pregna-5, 7-dien-20-one (5k) to the 9β, 10α-isomer (5ℓ) from which biologically active 6-dehydro-9β, 10α-progesterone (64)[9] was prepared.

The present study has involved an investigation of the chemistry of 10α-steroid derivatives, directed towards the synthesis of potentially useful unnatural steroid analogues. In particular we have attempted to prepare 5-oxygenated-10α-steroidal compounds in order to investigate the effect of the configuration about the C(9) - C(10) bond on the course of acid catalyzed elimination reactions of 5-oxygenated steroids.

DISCUSSION

The pyrolysis of vitamin D_3 (7b) gave 9β-cholesta-5, 7-dien-3βol (5i) and 10α-cholesta-5, 7-dien-3β-ol (5h). The 10α-isomer was used in this work and the 9β-isomer in a concurrent project.[86]

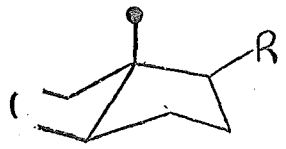
Acetylation of the 10α-dien-3β-ol (5h) gave 10α-cholesta-5, 7-dien-3β-yl acetate (5m) which had data compatible with that reported by Windaus et al[29] for the acetate of their "pyro-vitamin D_3". Although the structure of the dienol (5h) has not been rigorously established it follows by analogy with the D_2 series. The angular methyl resonances of the dienes (5h, 5m, 5i) compare well with that expected from published data in the D_2 series[34]. (Table 1).

TABLE 1

Compound	$C^{18}H_3$ δ (ppm)	$C^{19}H_3$ δ (ppm)	Refs.
10α-cholesta-5, 7-dien-3β-ol (5h)	0.55	1.10	(a)
10α-cholesta-5, 7-dien-3β-yl acetate (5m)	0.56	1.075	(a)
10α-ergosta-5, 7-dien-3β-yl acetate (5n)	0.575	1.075	(b)
9β-cholesta-5, 7-dien-3β-ol (5i)	0.64	1.24	(c)
9β-ergosta-5, 7-dien-3β-yl acetate (5e)	0.65	1.26	(b)

(a) This thesis (b) Ref. 34 (c) Ref. 86

Differences in chemical shift between the 10α-isomers (5h, 5m, 5n) are slight and can be accounted for by substituent effects. The steric relationship of the side chain to the C(13)-methyl is the same as in the natural steroid skeleton (Fig. 11).

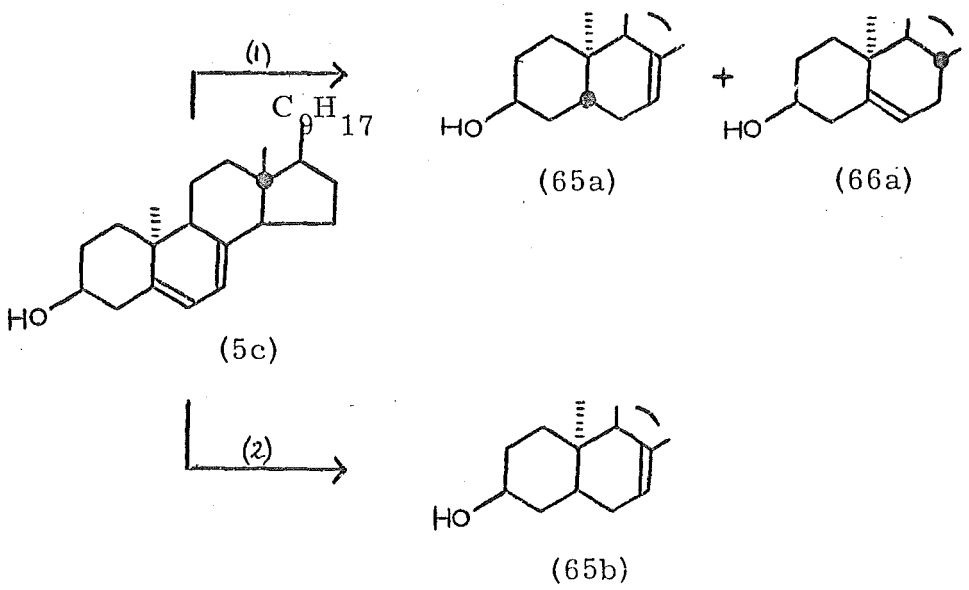


-Fig. 11-

In the natural series the 17β-C_8H_{17} group shields this methyl by 0.01 ppm relative to the 17β-C_9H_{17}[87]. Similarly the relative influence of these side chains on the C(10)-CH_3 chemical shift is expected to be small, there is no direct analogy with the natural series but the side chain and C(10) -methyl are well separated in each instance. Therefore the diene acetate (5m) is expected to exhibit methyl resonances at similar chemical shifts observed for the D_2-analogue (5n). A similar argument applies to the 9β-isomers (5i) and 5(e). There is sufficient difference between the 9β- and 10α-isomers (i.e. δ 0.57, 1.057 ppm versus δ 0.65, 1.26 ppm) to make a confident structural assignment to the dienols (5h, 5i) on the basis of NMR. The influence of varying the C(3)

-substituent on the angular methyl shifts is as expected from data in the natural series. For example, in the 9β-isomers (5i) and (5e) the difference in C(10)-methyl shift is accounted for by the variation at C(3).

Jones et al[88] have reported both Δ^5- and Δ^7-olefinic products from reductions of 10α-ergosta-5,7-dien-3β-ol (5c), (Fig. 12). The relative amounts of the Δ^7-(65a) and



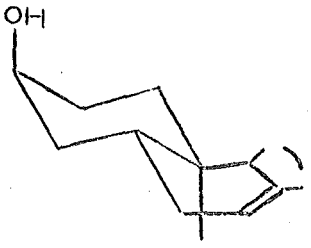
(1) Na or Li/NH_3/EtOH. (2) H_2/Ni/EtOH or Na/EtOH.

-Fig. 12-

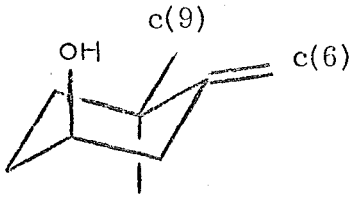
Δ^5-(66a) olefins from the metal-ammonia reduction depended on the metal and the dryness of the reaction media. With sodium only Δ^7-olefin (65a) was formed but with lithium both

the Δ^7-5β-olefin (65a, 46%) and the 8β-Δ^5-isomer (66a, 15%) were isolated. In a carefully dried reaction media the yield of each isomer (65a, 66a) was 35%. In the present work, however, it was found that the lithium-ammonia reduction of 10α-cholesta-5, 7-dien-3β-ol (5h) gave 5β- and 5α-cholest-7-en-3β-ol (65c, 65d) in 63% and 15% yield respectively.

The NMR spectrum of the minor product exhibited "one proton" resonances at δ 5.15 ($W_{h/2}$ 7Hz) and δ3.78 ($W_{h/2}$ ca 15Hz)ppm characteristic of an isolated trisubstituted double bond and an equatorial secondary hydroxyl respectively. From Dreiding models it can be shown that the 8ξ-Δ^5-olefins (66b, c) and 5β-Δ^7-olefin (65c) have a rigid structure with an axial C-(3)-hydroxyl function, (Fig. 13). However the 5α-Δ^7-olefin (65d) has a flexible structure[88,89] and could exist



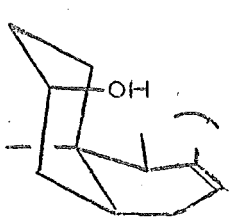
(65c)



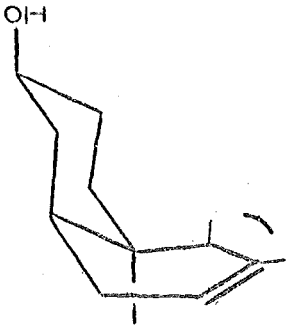
(66b, c)

-Fig. 13-

in either of the conformations shown in (Fig. 14). Conformer



conformer x



conformer y

-Fig. 14-

(y) has an equatorial hydroxyl function and on this basis the minor product was assigned as 5α, 10α-cholest-7-en-3β-ol (65d). Jones et al[88] observed that each of the 5α, 10α-ergosta-7, 22-dien-3ε-ols (65b , 65e) adopts the particular conformation in which the C(3)-hydroxyl function is equatorial; i. e. in this system the hydroxyl function has a dominant role in fixing the conformation. In the corresponding 9β 10α-derivatives (67a, 67b) a common conformation is adopted such that the hydroxyl is axial in the 3α-isomer (67a) and equatorial in the 3β-isomer (67b)[90].

The major product exhibits NMR data characteristic of a trisubstituted double bond (δ 5.18 ppm) and an axial hydroxyl function (δ4. 05 ppm, $W_{h/2}$ 8Hz). The acetate (65f)

derived from this dienol (65c) exhibits a multiple acetate band[91] in the infrared spectrum confirming the axial nature of the C(3) substituent. From the foregoing discussion this data is consistent with either the 8ε-Δ^5-olefin (66b, c) or 5β-Δ^7-olefin (65c) structures, (Fig. 13).

The 8β-Δ^5-structure (66c) can be ruled out on the basis of angular methyl signals; in the dienol (65c) these occur at δ 0.55 and 0.83 ppm whereas 10α-cholesterol (66c) exhibits these signals at δ 0.69 and 0.82 ppm[36]. Oxidation of the hydroxy-olefin (65c) with Jones reagent gave 10α-cholest-7-en-3-one (68). Ultraviolet and infrared spectral data indicated the presence of isolated carbonyl and olefinic functions. Adsorbtion on active alumina and treatment with methanolic hydroxide failed to effect conjugation of this ketone. This suggests the olefinic bond to be Δ^7- rather than Δ^5- and the hydroxy-olefin (65c) is thus assigned as 5β, 10α-cholest-7-en-3β-ol (65c).

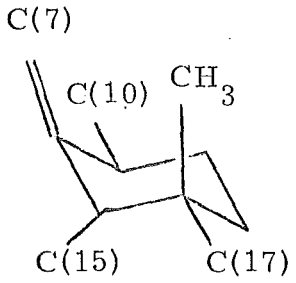
Both 5β, 10α-cholest-7-en-3β-ol (65c) and the acetate (65f) exhibit the $C^{18}H_3$ signal at approximately the same chemical shift as that in the natural analogues (69a, 69b). (Table 2). In each of these compounds the

TABLE 2

	$\delta(C^{18}H_3)$ppm
5β, 10α-cholest-7-en-3β-ol (65c)	0.52[a]
5β, 10α-cholest-7-en-3β-yl acetate (65f)	0.53[a]
5α, 10β-cholest-7-en-3β-ol (69a)	0.52[b]
5α, 10β-cholest-7-en-3β-yl acetate (69b)	0.53[c]
5α, 10α-cholest-7-en-3β-ol (65d)	0.55[a]

(a) This thesis. (b) Calculated value[88]. (c) Observed value[88].

immediate chemical environment of this methyl, particularly with respect to the shielding influence of the Δ^7-bond, is the same (Fig. 15). Indeed the difference between the

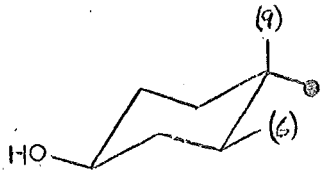


-Fig. 15-

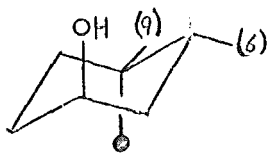
5β, 10α- and 5α,10β- isomers lies in the relationship of ring A (including $C^{19}H_3$) to this methyl. However the distance of this stereochemical variation from the C(13)-methyl is sufficient to make its influence on this methyl shift negligible. The

situation is similar to the natural steroid series where inversion at C(5) has no influence on the $C^{18}H_3$ chemical shift[92]. In the 10α-series inversion at C-5 from β- to α- causes a 0.03 ppm downfield shift, (cf data for (65c) and (65d)). The 5α, 10α-isomer (65d) has ring A perpendicular to and above ring B and thus much closer to the $C^{18}H_3$ group than in the 5β,10α (65c) and 5α, 10β (69a) isomers. In particular this methyl is now nearer the C(3)-hydroxyl and is also in the deshielding zone of the C(1)-C(2) bond.

Comparison with natural analogues is not possible for the $C^{19}H_3$ resonance since the local chemical environment of this methyl differs markedly between the 10β and 10α isomers. However the difference in the shift of this methyl in the cis- and trans-A/B isomers (65d, 65c) can be compared with this difference in the natural series. Inspection of Dreiding models shows that the difference in chemical environment between the A/B-cis-10α- and A/B-trans-10α- isomers (65d, 65c) lies in the relationship of this methyl to ring A. (Fig. 16). In the 5α-



5α, 10α- (65d)

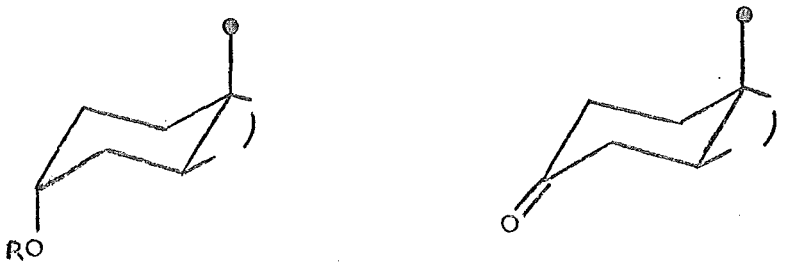


5β, 10α-(65c)

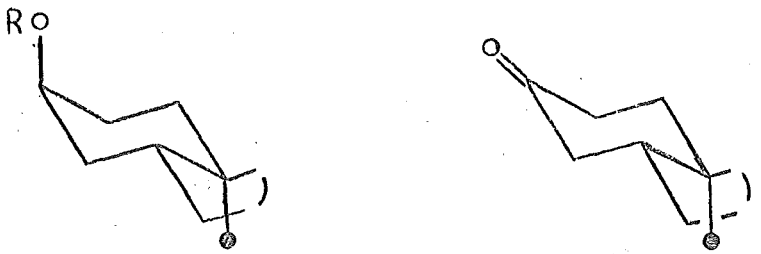
-Fig. 16-

isomer (65d) the methyl is equatorial to ring A and appears 0.1 ppm downfield of that in the 5β-isomer (65c) where it is axial. In the natural steroids the $C^{19}H_3$ group is equatorial to A in the A/B-cis isomers and appears ca 0.13 ppm downfield of the C(10)-methyl in the A/B-trans isomers where it is axial to ring A.[87, 92]

Although the absolute value of the $C^{19}H_3$ chemical shift in the 10α-isomers (65c, d) cannot be compared to that in a natural analogue it was possible to correlate substituent effects between the two series. (Fig. 17). The steric



5α, 10β-series



5β, 10α-series

-Fig 17-

relationship between the angular methyl and the C(3) substituent is the same in each series and the table shows a correlation between "additive shift values" derived in the natural series[87] and the variation in the 10α-methyl shift as the C(3)-substituent alters; (Table 3). This illustrates the general applicability of substituent effects derived in

TABLE 3

Compound	(a)	(b)
5β, 10α-cholest-7-en-3β-ol (65c)	0.83	0.00
5β, 10α-cholest-7-en-3βyl acetate (65f)	0.84	0.02
5β,10α-cholest-7-en-3-one (68)	1.07	0.24

(a) $\delta(C^{19}H_3)$ppm (b) additive shift value of substituent in natural analogue.[87]

the natural series[87] to analogous situations in unnatural isomers. Such correlations proved useful in structural assignments, especially for the saturated 5β, 8α, 10α- and 5α, 8β, 10α- compounds later in this thesis (Pp.56-76).

The failure to produce the Δ^5-olefins (66b, 66c) by direct reduction of the $\Delta^{5,7}$-dienol (5h) and a concurrent interest in the department in epoxy-olefins[93] led to attempts at epoxidation of the $\Delta^{5,7}$-diene moiety. It was hoped that

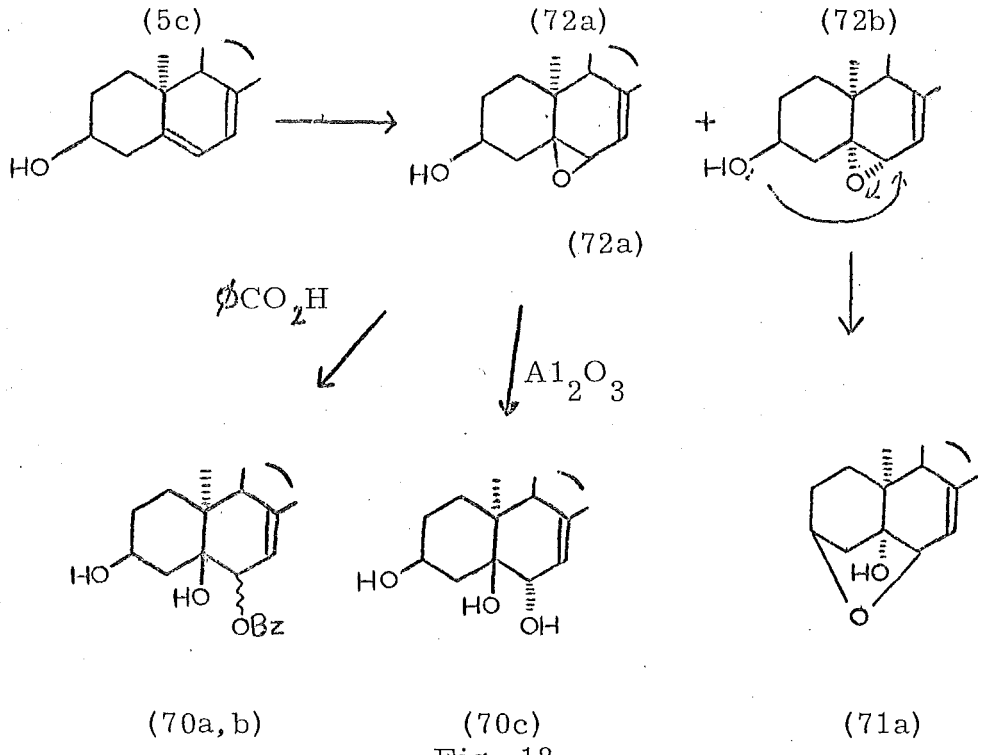
via the resultant epoxy-olefins it might be possible to synthesise saturated 5-oxygenated-10α-derivatives. The reaction of 10α-cholesta-5, 7-dien-3β-ol (5h) with monoperoxyphthalic acid took approximately two hours and produced a largely intractable product mixture which exhibited no spectral evidence for the presence of α,β -unsaturated epoxides.

Cragg and Meakins[94] have oxidized 10α-ergosta-5, 7-dien-3β-ol (5c) with perbenzoic acid in both long and short term reactions, (Table 4). The formation of the products was

TABLE 4

Peroxidation products from (5c)	(a)	(b)
5β, 10α-ergosta-7, 22-diene-3β-5, 6β-triol 6-benzoate (70a)	66%	19%
5β,10α-ergosta-7, 22-diene-3β, 5, 6α-triol 6-benzoate (70b)	14%	9%
5β,10α-ergosta-7, 22-diene-3β, 5, 6α-triol (70c)	-	36%
3β, 6β-oxido-5α, 10β-ergosta-7, 22-dien-5-ol (71a)	13%	12%

(a) yield after reaction time of 22hrs. (b) yield after 10min. reaction.



(70a,b) (70c) (71a)

-Fig. 18-

postulated to occur as in Fig. 18. Neither of the proposed intermediates (72a, 72b) were isolated.

Oxidation of 10α-cholest-5,7-dien-3β-ol (5h) with m-chloroperbenzoic acid in ether was complete in five minutes. Chromatography of the crude product gave two epoxides (A and B)*, an ether*, and polar mixtures. Epoxide (A) was obtained only in admixture with epoxide (B) and further attempts at chromatography gave diminishing amounts of epoxide and increasing amounts of polar mixtures. The other

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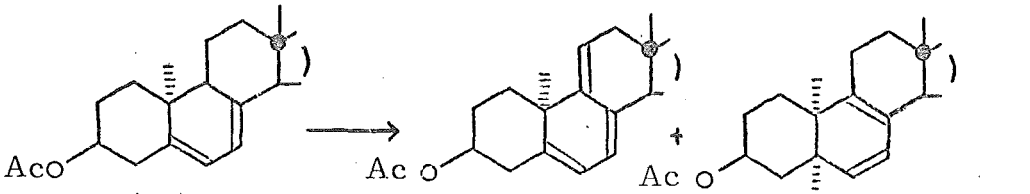
*spectral evidence

epoxide was also initially isolated in admixture with an ether; rechromatography of this gave three compounds which were later fully characterized as (72c), (71b) and (70d) respectively; (Pp.32-6).

Cragg and Meakins[94] found that acetylation of the 3β-hydroxyl profoundly affected the course of this oxidation (Fig. 19). Treatment of 10α-ergosta-5, 7, 22-trien-3β-yl acetate (5n) with perbenzoic acid gave 10α-ergosta-5, 7, 9(11), 22-tetraen-3β-yl acetate (73) and 5α, 10α-ergosta-6, 8(9), 22-triene -3β, 5-diol diacetate (74). However in the present work on



(5n) (73, 8%) (74, 86%)

-Fig. 19-

D_3-series it was found that the reaction produced approximately 24% of epoxide products*. These were obtained only in admixture and resisted attempts at separation by fractional recrystallization or chromatography.

The reaction of 10α-cholesta-5, 7-dien-3β-ol (5h) with perbenzoic acid in ether at 15°C for five minutes gave

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*NMR data on chromatography column fractions.

5,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c; 60%); 3β,6β-oxido-5α;10α-cholest-7-en-5-ol (71b; 12%) and 5β,10α-cholest-7-ene-3β,5,6α-triol (70d; 25%) after chromatography on 5% deactivated alumina. In several runs of this reaction there was evidence (NMR) of small amounts of benzoates in the product mixture. However it was found that in general the epoxide not only survived the reaction conditions* but was relatively stable to chromatography. Adsorption of the crude product on active alumina for four days gave the 3β,6β-ether (71b; 12%) and the 3β,5β,6α-triol (70d; 76%). A quantitative yield of the triol (70d) was obtained by adsorption of the epoxide (72c) on active alumina.

Elemental analysis of the ether (71b) is consistent with the molecular formula $C_{27}H_{44}O_2$. The NMR spectrum exhibits single proton resonances at δ4.23 ($W_{h/2}$ 7Hz), δ3.74 (J = 5c/s) and δ5.26 (J = 5c/s); double irradiation shows the latter two protons are coupled. This data indicates the presence of the CH-O- and C=CH-CH-O moieties; neither of

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*19 m. moles each of steroid and peracid in 300ml ether; 15°C, 5 min; cf. Cragg and Meakins - 3 m. mole of steroid and peracid in 30ml ether; 0°C; 10 min.

the oxy-functions is a secondary hydroxyl since the compound fails to acetylate even under forcing conditions. The infrared spectrum shows the presence of a hydroxyl, which must therefore be tertiary. Since the elemental analysis indicates the presence of only two oxygen atoms the structure must contain the -CH-O-CH-CH=C- moiety. A strong infrared absorbtion at 975cm^{-1} is consistent with the presence of an ether linkage[94,95]. The compound is stable on active alumina and could not be reduced with lithium aluminium hydride. Its structure was assigned as 3β,6β-oxido-5α,10α-cholest-7-en-5-ol (71b). This ether is thought to be formed as shown in Fig. 18 (P. 30).

The major product (72c) has the same molecular formula as the 3,6-ether (71b). A one proton signal at δ4.0 ($W_{h/2}$ 9Hz) ppm and acetylation under mild conditions indicates the presence of an axial secondary hydroxyl function. The NMR spectrum also shows two coupled doublets at δ2.31 ppm and δ5.42 ppm (J=4Hz) indicating the presence of a -C=CH-CH(O)-C- moiety.[96] The assignment of this compound as an epoxide was confirmed by its reactivity towards, and the products from, reaction on active alumina and lithium aluminium hydride reduction. The infrared spectrum exhibits peaks at 1275, 875, 860, 845, 822 cm^{-1} characteristic of a highly substituted epoxide[97].

This product was assigned as 5,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c); i.e. the D_3 analogue of one of the proposed intermediates (72a) in the oxidation of 10α-ergosta-5,7,22-trien-3β-ol (5c)[94].

The structure of the triol (70d) was assigned on the basis of the following data. Elemental analysis indicates a molecular formula of $C_{27}H_{46}O_3$. The NMR exhibits one proton' resonances at δ 4.23 ($W_{h/2}$ 10Hz), δ 3.74 (J= 5c/s) and δ 5.34 (J=5c/s; mild acetylation produces a diacetate (70e). This indicates the presence of an axial secondary hydroxyl and a C=CH-CH-OH moiety. The elemental analysis requires the presence of a tertiary hydroxyl. The presence of the allylic secondary hydroxyl is supported by the oxidation of triol (70e) to a dihydroxy-enone (70f)* with DDQ[98]. There are four possible structures which fit the above data; (Fig. 20). Each has an axial C(3)-hydroxyl and each has a dihedral angle of ca. 30° between the allylic and olefinic protons. However isomer

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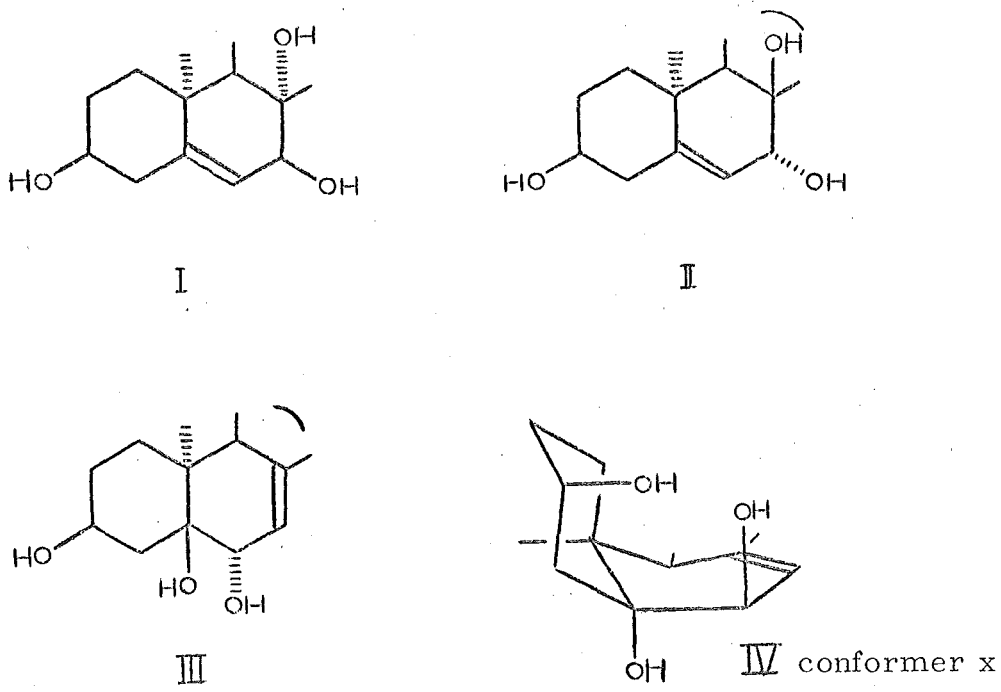
*Ref P. 40.



-Fig. 20-

IV is unlikely to adopt conformation x; earlier it was noted that 5α, 10α -cholest-7-en-3β-ol (65d) existed in conformation y (Ref. P. [23]). The presence of a 5α-hydroxyl should have little influence on this conformational preference - in either conformer it is axial to one ring and equatorial to the other. However the 6α-hydroxyl should make conformation x even less stable due to a 1, 3-diaxial clash of this hydroxyl with the C(9)-C(11) bond. Formation of isomer-II requires the initial epoxidation to occur on the β-face of the Δ^7-olefinic bond of the diene (5h); this position is severely hindered by the $C^{18}H_3$ group. The appearance of the $C^{18}H_3$ resonance

at δ0.52ppm indicates the presence of a Δ^7-olefinic bond* and is clearly incompatible with structure-II where the 8β-hydroxyl should markedly deshield this methyl. The triol (70d) is therefore assigned as 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d). Its mode of formation is indicated in Fig. 18, P. 30.

Reaction of 5, 6β-epoxy-5β, 10α-cholest-7-en-3β-ol (72c) with lithium aluminium hydride gave 5β, 10α-cholest-7-ene-3β, 5-diol (76a). The NMR spectrum exhibits a methine (δ4.05) and an olefinic (δ5.05) signal; a 'two proton' signal at δ3.22 ppm was removed by shaking a sample with D_2O. The infrared spectrum was obtained for a dilute solution in carbon tetrachloride. It exhibited hydroxyl bands assigned as follows - 3561cm^{-1} (C(3)-OH 'bound' to C(5)-OH); 3621cm^{-1} (C(5)OH 'bound' to C(3)OH and the olefinic bond), 3641cm^{-1} (free hydroxyls)[99]. Oxidation of this diol (76a) with chromium trioxide-pyridine gave 5-hydroxy-5β, 10α-cholest-7-en-3-one (76b). Spectral and analytical data is in accord with this formulation. The C$^{19}H_3$ signal is 0.23ppm downfield of that in the 3β, 5β-diol (76a) in the natural series oxidation of a 3α-hydroxyl function shifts the C$^{19}H_3$ signal downfield by ca 0.24ppm[87]. The position

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*Ref. Table 2. P. 25.

of the olefinic bond at C(7)-C(8) rather than C(5)-C(6) was confirmed by the stability of this compound to attempted base catalyzed isomerization. This provides additional confirmation of the structures assigned to the epoxide (72c) and the triol (70d).

The diol (76a) was also oxidized with Jones reagent to give the hydroxy-ketone (76b, 37%) and 5-hydroxy-5β, 10α-cholest-7-ene-3, 6-dione (77; 30%). Spectral data for the dione indicated an isolated ketone function (1715cm^{-1}), a tertiary hydroxyl (3450cm^{-1}; no CHOH signal in NMR) and an enone moiety (δ5.73 ppm; λ_m 1675cm^{-1}). The assigned structure was confirmed by oxidation of 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d) to the same dione (77). Treatment of the diol (76a) with Jones reagent for a longer reaction time gave the hydroxy-dione (77, 30%) and 10α-cholest-4, 7-diene-3, 6-dione (78, 26%). Mass spectral and infrared date showed the absence of the C(5)-hydroxyl in the latter product, and the NMR spectrum exhibited two sharp signals in the enone region. The infrared spectrum showed absorbtions at 1690 cm^{-1} and 1650 cm^{-1} consistent with the presence of the α,β-unsaturated and α,β-$\alpha'\beta'$ unsaturated carbonyl functions.[100,*] An ultraviolet

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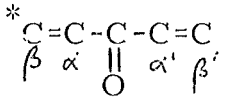
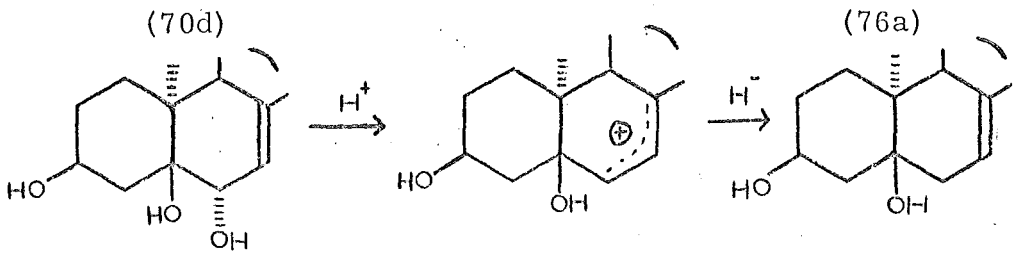


maxima at 306 nm was also in accord with the assigned structure.[101]

Hydrogenation of Δ^7-natural steroids is difficult and is often complicated by isomerization to the even less reactive $\Delta^{8(14)}$-isomers[102]. However such olefins have been hydrogenated via prior isomerization to the reactive Δ^{14}-isomers[102,103]. 9β-Δ^7-olefins[104-7] do not isomerize under hydrogenation conditions and they hydrogenate more readily than their natural analogues giving 8β-products[54,86,104,105,106]. 5β,9β-cholest-7-ene-3β,5,6β-triol(79) was hydrogenated in a week at normal temperature and pressure in ethanol using Adams catalyst[86]. Inspection of Dreiding models shows that the $C^{18}H_3$ group severely hinders the β-face of Δ^7-olefins in the natural series; inversion of the configuration at C(9) reduces this hindrance and hydrogenation of 9β-Δ^7-olefins occurs from the β-face. In their study of the reduction products of 10α-ergosta-5,7,22-trien-3β-ol (5c) Jones et al found the Δ^7-olefins were resistant to hydrogenation under forcing conditions in neutral media[88]. Attempted hydrogenation of 5α,10α-ergosta-7,22-dien-3β-ol (65b) in acetic acid produced 5α,10α-ergost-8(14)-en-3β-yl acetate (80a) which was readily reduced in an acetic acid-hydrochloric acid media to 5α,10α-ergostan-3β-yl acetate (81a); in acetic acid-perchloric acid the product was 5α,10α-ergostane (81b)[88].

Attempted hydrogenation of 5β,10α-cholest-7-ene-3β, 5,6α-triol (70d) in ethanol was not successful. In acetic acid the major product was 5β,10α-cholest-7-ene-3β,5-diol (76a; 35%), identical to a sample prepared from lithium aluminium hydride reduction of 5,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c). Under the acidic conditions, cleavage of the



-Fig. 21-

C(6)-O bond gives an allylic carbonium ion which is then reduced to the diol (76a) (Fig. 21). During one attempt at this hydrogenation a product assigned as 5β,10α-cholest-7-ene-3β,5,6α-triol 6-acetate (70g) was obtained in ca 25% yield; however this product was only observed once and obtained only in admixture with other compounds. The assignment of the structure was based on NMR spectral data. The acetate function (characterized by a methyl signal at δ 2.02 ppm) was identified as being allylic by the appearance of one proton doublets at δ 5.02 ppm and δ 5.26 ppm. (J_{obs} = 5c/s). The 3β-hydroxyl function was characterized by a methine resonance

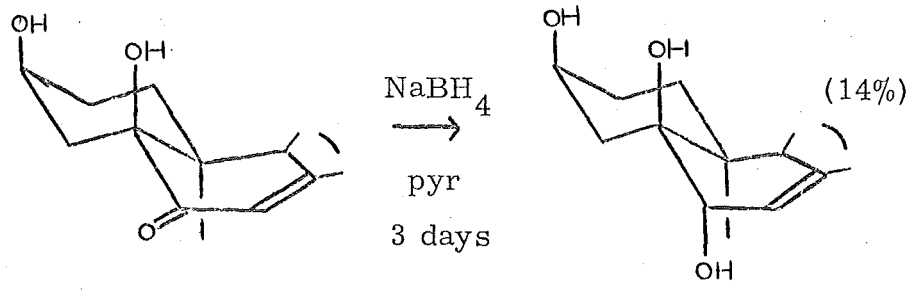
at δ4.23 ppm ($W_{h/2}$ 8Hz). Another product (ca 15-25%), also obtained in admixture, was not fully characterized or identified. NMR data of chromatography column fractions indicated this compound to have methyl signals at δ0.7 and 1.0 ppm, and a methine signal at δ3.58 ppm. The purer fractions were combined and recrystallized but both the melting point and elemental analysis indicated the sample to be impure. These fractions were treated with ozone followed by zinc in acetic acid; the crude product showed an infrared absorbtion at 1715 cm^{-1}. The remaining products of hydrogenation were obtained as intractable and unidentified mixtures which were not perservered with. It was decided not to attempt hydrogenation under the strongly acid conditions used by Jones et al[88] for reduction of the 10α-ergost-7-enes; the presence of tertiary and allylic hydroxyl functions would give too many competing reactions under these conditions. Attempts at hydroboration of 5β,10α-cholest-7-ene-3β,5,6α-triol (70d) were not successful.

In view of these difficulties in hydrogenating the triol (70d) it was decided to look at reductions of the related enone (70f). Oxidation of 5β,10α-cholest-7-ene-3β,5,6α-triol (70d) with 2,3-dichloro-5,6-dicyano-benzoquinone gave 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f). Identification

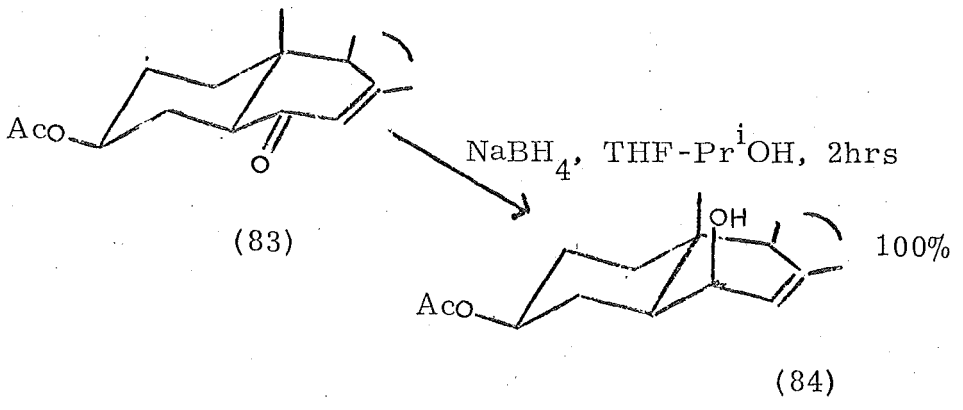
of this product followed from the known selectivity of the oxidant[98] and was confirmed from spectral data. The enone moiety was characterized by ultraviolet (λ_m 240nm) and infrared (ν_m 1680, 1630 cm^{-1}) spectra; the presence of the 3β-hydroxyl was indicated by the CHOH signal at δ4.27 ppm in the NMR spectrum; and the presence of the tertiary hydroxyl follows from elemental analysis.

Enones have been observed to be more amenable to hydrogenation than isolated double bonds;[108] for example the normally resistant $\Delta^{8(9)}$ and $\Delta^{8(14)}$-olefins in the natural series are readily hydrogenated when in conjugation with a ketone function[108]. Hydrogenation of Δ^{7}-6-ketones in the natural series results in the formation of 8β-6-ketones[109]. Hydrogenation of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f) under mild conditions, however, gave no reaction. It has also been found that in complex metal hydride reductions of enones both the olefinic bond and the carbonyl function may be reduced[110]. In particular the use of sodium borohydride in pyridine can give high, even quantitative, yields of such products[111-113]. Treatment of progesterone (4b) with this reagent at room temperature for four and a half hours gave 5α-pregnane-3β,20β-diol (82) in quantitative yield[111]. However the reaction of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f)

with sodium borohydride-pyridine for three days gave mainly unreacted enone (66%) and 5β,10α-cholest-7-ene-3β,5,6α-triol (70d; 14%). The C(6) hydroxyl function produced in this reaction is pseudo-axial. This stereochemistry is also observed in the borohydride reduction of the natural analogue, 6-oxo-5α-cholest-7-ene-3β,5-diol, 3-acetate (83)[114]; Fig. 22.



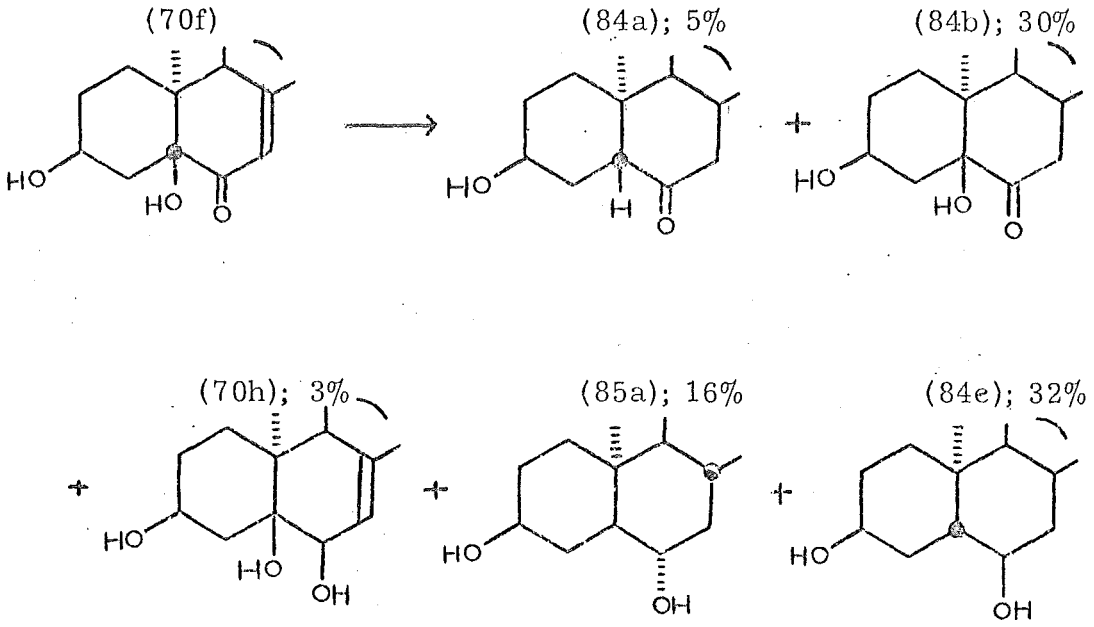
(70g) (70d)



(83) (84)

-Fig. 22-

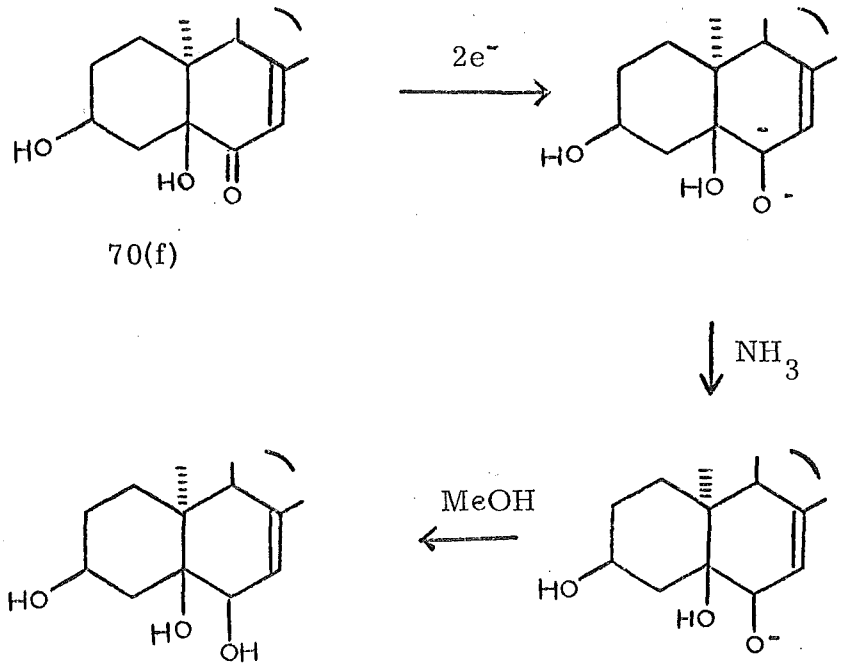
At this stage it was decided to investigate dissolving metal reductions of the enone (70f). A preliminary investigation of the reduction with sodium-amyl alcohol led to an intractable mixture of an indeterminate number of products. The reduction of 3β, 5-dihydroxy-5β, 10α-cholest-7-en-6-one (70f) with lithium-ammonia using methanol to quench the reaction gave the products shown in Fig. 23. Also recovered was an unidentified non-polar mixture in approximately 4% yield. This reduction leads to the creation of up to three new asymetric



-Fig. 23-

centres and configurational assignments were made on the basis of NMR data of the products and their derivatives. Of particular importance was the variation of the $C^{19}H_3$ chemical shift as the substituents at C(3) and C(6) were altered. The magnitude of incremental shifts expected in different possible skeletal structures were assessed by drawing analogies with the natural series where "substituent effects" are well documented.[87,115] A full discussion of the determination of the structures of these products is given on Pp. 56-76.

10α-Cholest-7-en-3β,5β,6β-triol (70h) arises from a 1,2-addition to the 6-keto function (Fig. 24)[116] and is protected from further reduction since it exists as an oxyanion until the reaction is quenched. This triol (70h) survives the quenching procedure since destruction of excess reductant occurs before significant reduction of the allylic C(6)-hydroxyl can occur. It may be, of course, that some of the non-polar compounds (ca 4%) arise from this triol. Unlike the borohydride reduction this reaction produces the thermodynamically more stable equatorial C(6)-hydroxyl.

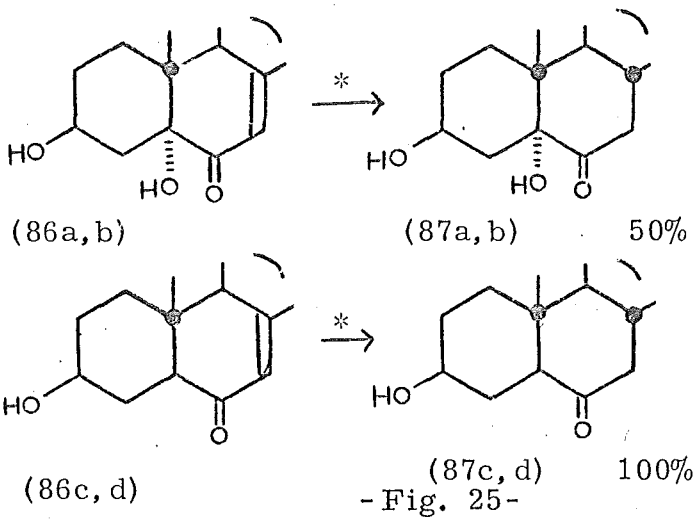


70(f)

70h, 3%

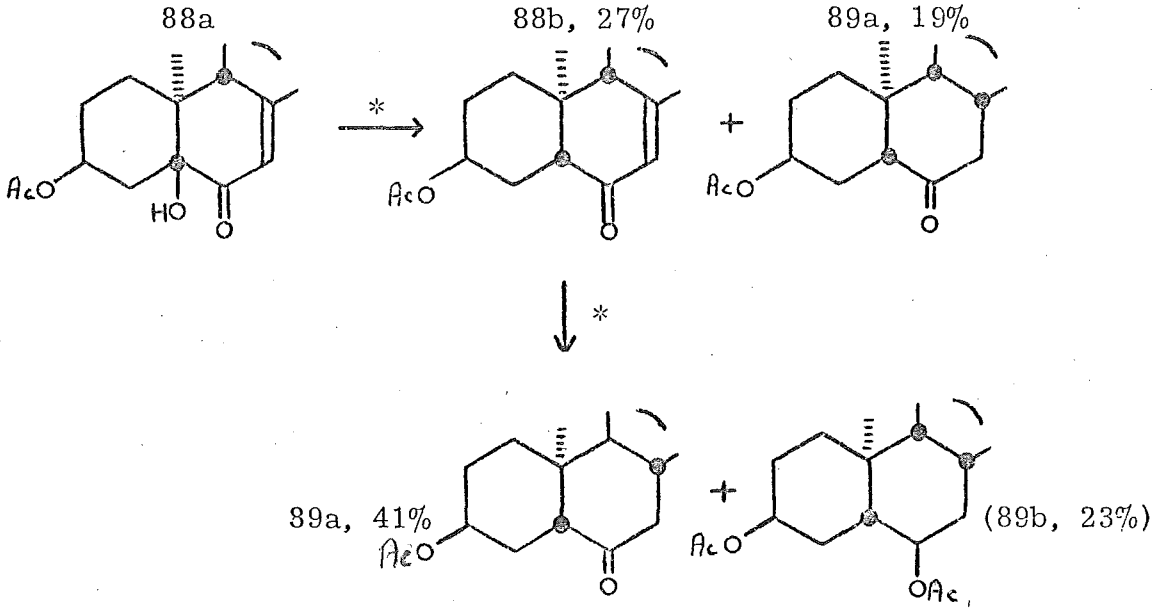
-Fig. 24-

The major reaction paths involve "1, 4 reduction"[117] of the enone function with or without concomitant loss of the tertiary hydroxyl function. In the natural series the lithium-ammonia reduction of 5α-hydroxy-7-en-6-one moiety was found to give the corresponding 5α-hydroxy-6-one with the newly created asymmetric centre at C(8) having the thermodynamically more stable 8β-configuration[118]. (Fig. 25).



-Fig. 25-

Similarly the reduction of the 5-deoxy-enones (86c, 86d) gave quantitative yields of the 5α, 8β-6-ketones (87c, 87d)[118]. In the 9β, 10α- series the reduction of 6-oxo-9β, 10α-ergosta-7, 22-diene-3β, 5β-diol, 3-acetate (88a) has been reported to give 5-deoxy-products[119]; (Fig. 26).

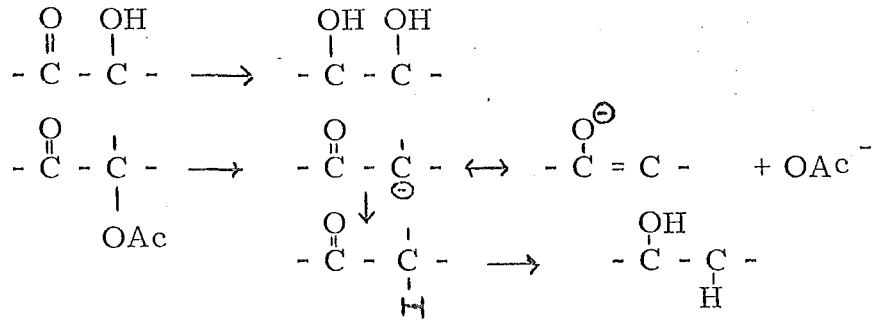


-Fig. 26-

*Reagents 1. Li-NH_3 2. NH_4Cl 3. Ac_2O-pyridine

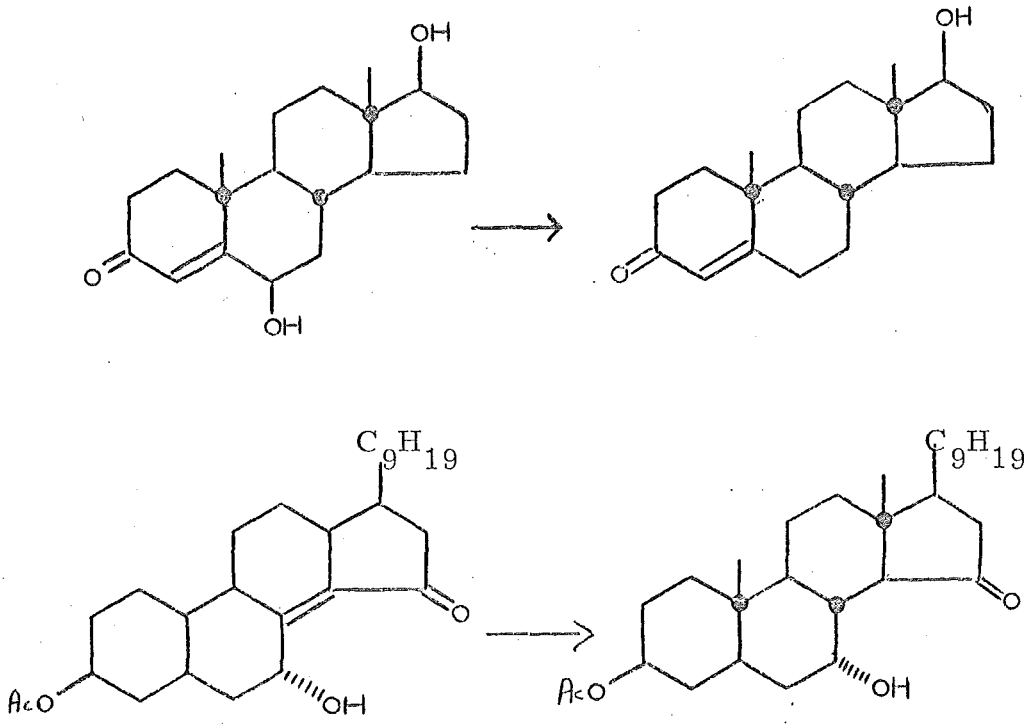
Unlike the result obtained in the present study (Fig. 23) no A/B-cis-5-deoxy products were reported, but only 46% of the starting material (88a) was accounted for. The stability of the ketones (88b, 88a) to base conditions was evidence for the 5β-configuration and the C(8) configuration in (89a, 89b) was assumed to be the more stable 8β-configuration.[118, 119] There was no independent confirmation of the structures assigned. Zurcher has reported the lithium-ammonia reduction of 3β,5-dihydroxy-5α-ergosta-7,9(11)-dien-6-one (90) to 5β-ergostane-3β,6α-diol (89c)[120].

It has been found that dissolving metal reductions of ketols produce diols whereas ketol acetates give ketones or alcohols[121]. The ketol acetate reduction is regarded as proceeding by a reductive cleavage followed by proton addition to the resultant enolate anion[122] and possibly further reduction of the ketone function (Fig. 27).



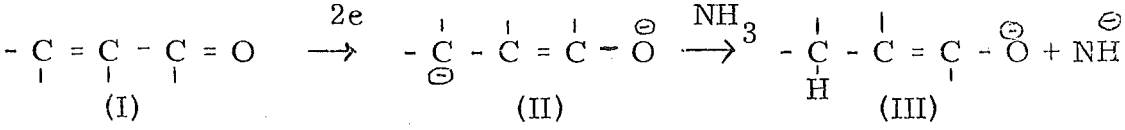
-Fig. 27-

However it appears that conjugation of the ∝-ketol function with a double bond makes loss of the ∝-hydroxyl more likely. A related reaction is the reduction of vinylogs of ∝-ketols (Fig. 28)[123, 124].



-Fig. 28-

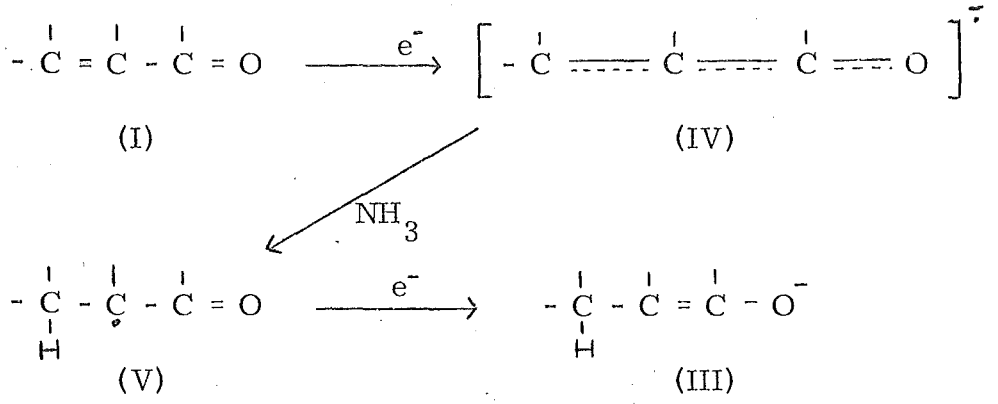
Dissolving metal reductions of enones, first reported by Wilds and Nelson[125], have been extensively documented. Originally reduction was proposed by proceed via the dianion (II)[118] (Fig. 29), but it is now accepted that protonation occurs



-Fig. 29-

after the addition of one electron to the enone (Fig. 30)[126].

A similar mechanism was also recently postulated by House[127].



(I) (IV) (V) (III)

- Fig. 30 -

If the enolate anion (III) is not protonated while there is reductant present then the product obtained is a saturated ketone. However if the reduction is carried out in the presence of a proton donor then the major product is a saturated alcohol. Often the use of proton donors to quench the reduction leads to considerable over-reduction. The extent of this depends on the relative rates of ketone reduction and destruction of reductant by the proton source[128]. In the present work (Ref. P. 43) the use of methanol to quench the reduction led to the formation of fully reduced products in 46% yield.

Barton and Robinson[118] observed that these reductions produced the thermodynamically more stable configuration at the β-carbon of the enone moiety.* Indeed the dissolving

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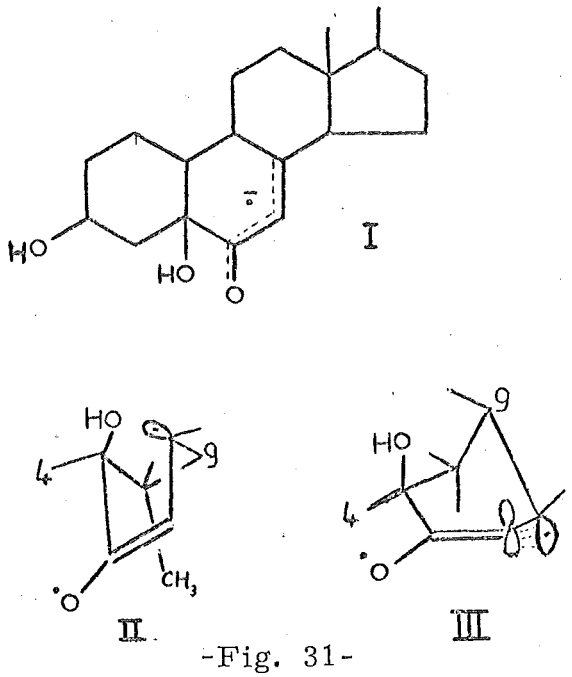
* C = C - C = O
(β) (α)

metal reductions of enones in the natural steroid series do give predominantly if not exclusively[129] the thermodynamically favoured products. Stork and Darling[126,130] examined the reduction of octal-1,(9)-en-2-ones (94) and concluded that the β-carbon configuration of the products corresponded to the more stable configuration of the β-carbanion intermediate in which overlap of the β-carbon and enol orbitals is maintained. This means that the product is the most stable of the isomers in which the newly introduced hydrogen is axial to the ring containing the ketone. In natural steroids this in fact corresponds to the stablest β-carbon configuration, as per Barton and Robinson[118], and this is also the case in the 10α-steroids (Ref. Pp. 54-5). The products reported for the reduction of 6-oxo-5β, 9β, 10α-ergosta-7, 22-diene-3β, 5-diol 3-acetate (88a) and 6-oxo-5β, 9β, 10α-ergosta-7, 22-dien-3β yl acetate (88b), Fig. 25, were assigned the 8β configuration on the basis of the Barton and Robinson generalization[118]. However the 8β, 9β, 10α-structure has the C(8) proton equatorial to the ring containing the ketone function. It would seem that these structural assignments would now require independent confirmation.

The reaction products from the lithium-ammonia

reduction of 3β, 5-dihydroxy-5β, 10α-cholest-7-en-6-one (70f), (Fig. 23), can be rationalized in terms of the above discussion of enone and ketol reductions. Addition of an electron to the enone moiety gives the radical anion (I, Fig. 31) which is then protonated on the α-face. Inspection of Dreiding models of isomers of the anion, with the carbanion centre regarded as tetrahedral shows the '8α' isomer to be the more stable (Fig. 31). The '8β anion' has a pseudo-boat ring B



-Fig. 31-

where the C(8) anionic orbital is not perpendicular to the enolate bond (C(6), C(7)). Furthermore this anion is destabilized by the 5β-hydroxyl, or 5-oxy-anion. This latter factor has been noted in the lithium-ammonia reduction of

1-methoxy-6aα, 8β-dihydroxy-10a-methyl-5, 6, 6a, 7, 8, 9, 10, 10a, 11, 12-decahydro-chrysene (95) to 1-methoxy-6aα, 8β-dihydroxy-10a-methyl-4b, 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11, 12-dodecahydro-chrysene (96) in which the 6aα-hydroxy-function directs the protonation at C(10b) and produces a product which is not the thermodynamically more stable[131]. The '8α' anion' (III) has a pseudo-chair ring B with the C(8) and enol orbitals near perpendicular and the carbanion at C(8) well removed from the C(5)-oxy function. Therefore the product of direct enone reduction is the 8α-enolate anion (97), which then forms 3β5-dihydroxy-5β, 8α, 10α-cholestan-6-one(84b) upon addition of methanol. There was no over reduction to the corresponding triols. (84c, 84d)

The 5-deoxy products are considered to arise from initial reductive fission of the 5β-hydroxyl function (Fig. 32) followed by reduction of the enone moiety. The loss of the hydroxyl is contrary to the normal experience with α-ketols.[121] However in this particular case the ketol moiety is conjugated to an olefin and the hydroxyl is tertiary. It may be that whereas the hydroxyl is usually protected from reductive fission by formation of alkoxide ion in this case its tertiary position hinders this reaction and electron addition to the

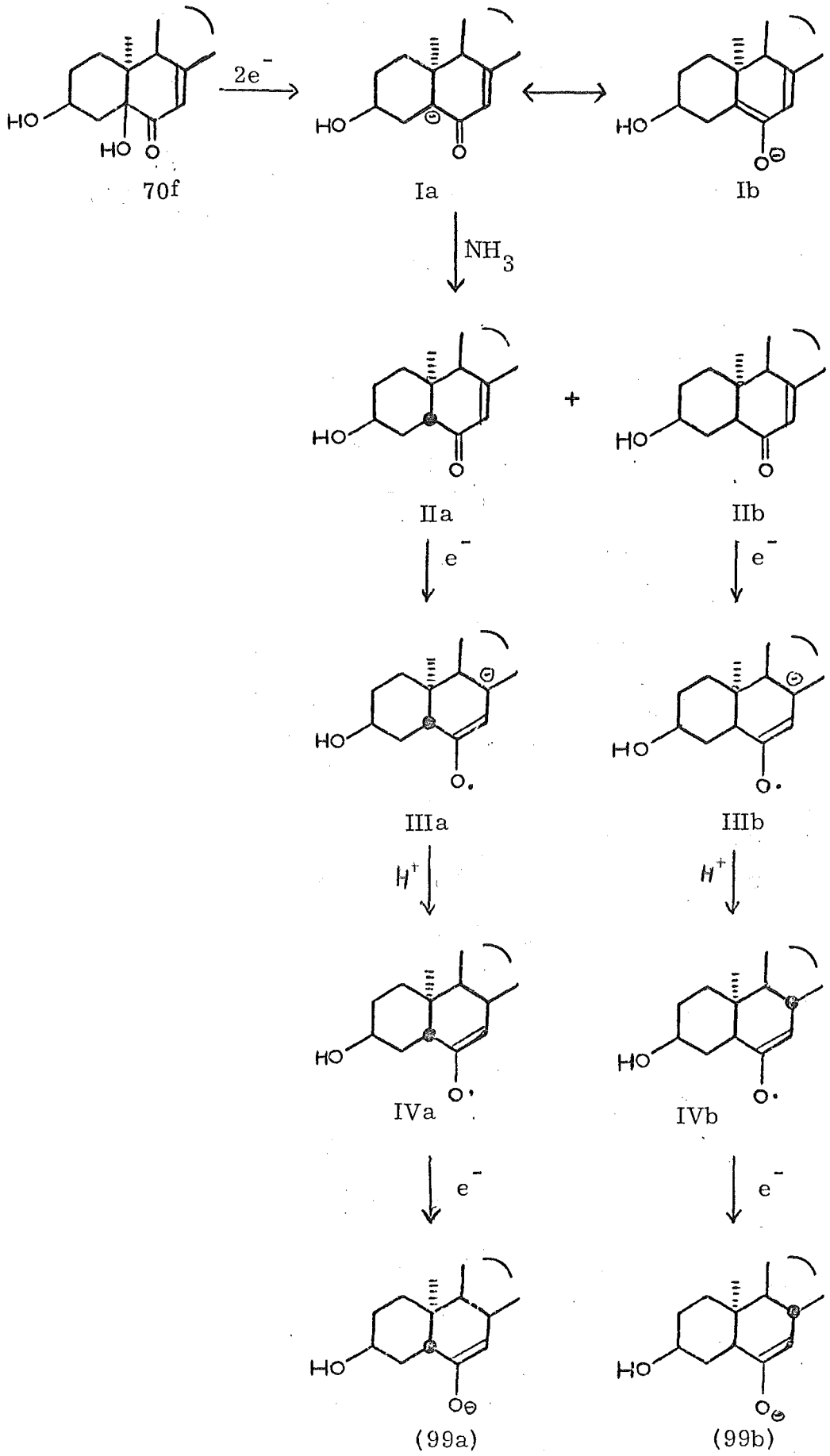
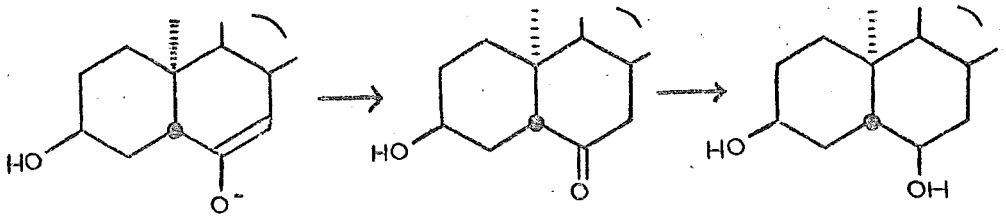


Fig. 32.

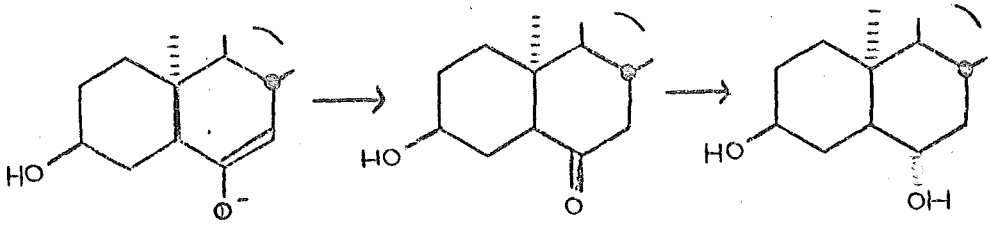
C(5)-O bond becomes competitive. (Also, in general, α-carbanions of enolates are not protonated by ammonia[132] (I → IIa + IIb) but in this the enolate is conjugated to an olefinic bond (Δ^7)). Unlike the result reported in the retro-series (Fig. 25, P. 40) both the A/B cis and trans isomers are formed. Indeed a considerable amount (14%) of A/B cis isomer appears as diol (85a) in the product mixture. Reduction of the deoxy-enones (IIa, IIb) then leads to the enolates (99a, 99b). The 5β-radical anion (IIIa) protonates at C(8) from the α-face for the reason discussed earlier for the 5β-hydroxy analogue (Fig. 31, P. 51). The 5α-radical anion (IIIb) protonates at the 8β-position, no 5α, 8α-isomer being isolated. Both the 5α, 8β- (85b) and 5α, 8α- (98) ketones have the newly introduced C(8)-proton axial to ring B but the '5α, 8β' isomer (85b) is the more stable. The all chair 5α, 8α-isomer (98) has rings A and C perpendicular to ring B giving rise to a large steric interaction between the C(9)-C(11) bond and ring A, alternate conformations in which this strain is relieved require ring B to adopt a boat or skew conformation. The 5α, 8β-isomer has rings B and C coplanar in the all chair form. As in the natural steroids the proton introduced at C(8) in the 5α, 10α- and 5β, 10α- enolates

(99a, 99b)* is axial to B in the stabler configuration; i.e. in these instances Stork and Darlings generalization[126,130] is equivalent to that of Barton and Robinson[118].

Upon addition of methanol the enolates (99a, 99b) undergo reduction to the C(6) alcohols (84e, 85a) via the corresponding ketones (84a, 85b), Fig 33.



(99a) 84a, 5% 84e, 32%



99a 85b, o% 85a, 16%

-Fig. 33-

It would appear that the reduction of the ketones (84a and 85b) is rapid enough to successfully compete with comcomitant

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*Fig. 32.

destruction of the reductant. The A/B trans-C(6) ketone (84a) was isolated in 3% yield and the A/B cis-C(6)-ketone was not isolated at all, however it is possible that some is present in the unidentified non-polar fractions (4%). In each instance the 6-ketone function reduces to a C(6) equatorial hydroxyl; this is general[133] for the reduction of ketones under these conditions although exceptions have been noted[133].

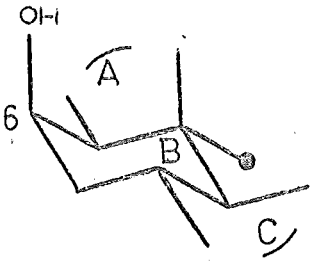
The mass spectrum of 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a) indicates a molecular formula of $C_{27}H_{46}O_2$; NMR and infrared spectra show the presence of an axial secondary hydroxyl function (δ4.15ppm $W_{h/2}$=7Hz, ν_m3450cm^{-1}); the ketone function is characterized by infrared (ν_m1695cm^{-1}) and ultra-violet and circular dichroism (λ_m283nm) maxima. The compound was therefore assigned as a 3β-hydroxy-5ξ, 8ξ, 10α-cholestan-6-one. Acetylation gave 6-oxo-5β, 8α, 10α-cholestan-3β-yl acetate (84f) characterized by an equatorial methine signal (δ5.15ppm, $W_{h/2}$ 8Hz), carbonyl absorbtions at 1740 and 1720cm^{-1} and a multiplet acetate band[91] at 1240cm^{-1} (i.e. axial acetate)[91]. This compound, and the dione (84g) and diacetate (84h) derivatives, show no evidence of a hydroxyl in infrared or NMR spectra confirming

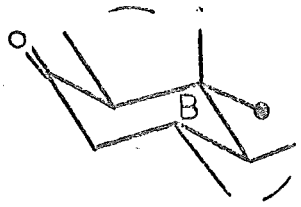
the 5-deoxy structure assigned above. An inspection of Dreiding models showed that all four possible stereoisomers (i.e. 5ξ, 8ξ)* could have an axial C(3) hydroxyl.

Reduction of the ketone (84a) with lithium aluminium hydride gave 5β, 8α, 10α-cholestane-3β, 6α-diol (84i) which exhibits equatorial methine resonances at δ 4.17($W_{h/2}$ 7Hz) and 3.72($W_{h/2}$ 6Hz)ppm. Acetylation of this diol (84i) produced 5β, 8α, 10α-cholestane-3β, 6α-diol diacetate (84h) which exhibited equatorial methine resonances in the NMR spectra and a multiplet acetate band in the infra-red spectra. The observation that both the C(3)-OR and C(6)-OR functions are axial in the diol (84i) and its diacetate (84h) means that the stereochemistry is either 5β, 8α, 6α or 5α, 8β, 6β since these are the only two 5ξ, 6ξ, 8ξ-isomers in which this condition is fulfilled.

A comparison of the $C^{19}H_3$ chemical shifts in the diol (84i) and hydroxy-ketone (84a) shows that the C(6)-hydroxyl deshields this methyl by 0.27ppm relative to the 6-ketone. In the 5α, 8β-isomers (85c, 85d) the steric relationship between the $C^{19}H_3$ group and the C(6)-substituents is comparable to that between this methyl and the C(4)-substituents in 4α-hydroxyls and C(4) ketones in the 5β-natural steroids, (Fig. 34). From Zurcher's "additive shift values"[87] for this

*The all chair conformation of the 5α, 8α isomer does not, however in view of the instability of this conformation (Ref. P. 54) the 5α, 8α-isomer may in fact exist in a chair-boat-chair or chair-skew-chair form.

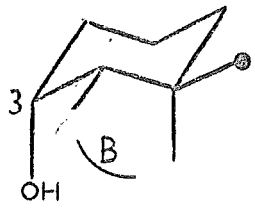


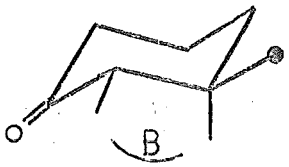


5α, 10α:

3β, 6β-diol (85c)

3β-hydroxy-6-ketone (85d)



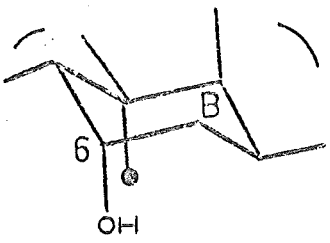


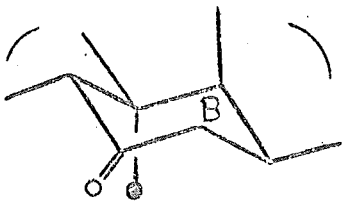
5β:

4α-hydroxy-

4-ketone

Fig. 34.

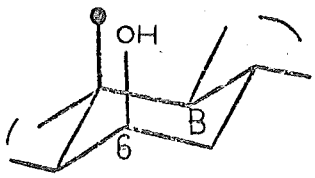


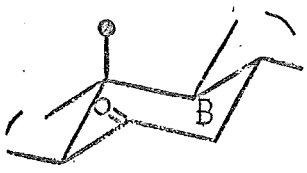


5β8α10α:

3β, 6α-diol (84i)

3β-hydroxy-6-ketone (84h)





5β:

6β-hydroxy

6-ketone

Fig. 35.

series the C(4)-ketone function deshields the $C^{19}H_3$ group by 0.19ppm more than the 4α-hydroxyl function does. This is not observed in the case of the diol and hydroxy-ketone under discussion, where it is the hydroxyl which has greater deshielding influence. In the 5β,8α-isomers (84i, 85a) the relationship between the $C^{19}H_3$ group and C(6)-substituents is comparable to that in natural A/B trans-steroids with a 6β-hydroxyl or 6-keto function (Fig. 35). From "Zurcher values"[87] the C(6) hydroxyl deshields the $C^{19}H_3$ group by 0.275ppm relative to a C(6) ketone. Consistent with these observations the '5β,8α,10α' skeleton was assigned to the hydroxy-ketone (84a) and its derivatives.

The assignment of the methine signals in the NMR of diol (84i) follows by a comparison with the hydroxy-ketone (84a). Both exhibit a signal at ca δ4.15ppm assigned to the C(3)- proton; the higher field signal (δ3.72ppm) in the diol is therefore assigned to the C(6)-proton. Similarly, in the diacetate (84h) the C(6)-proton signal is at a higher field than the C(3)-proton.

Chromium trioxide-pyridine oxidation of the hydroxy-ketone (84a) gave 5β,8α,10α-cholestane-3,6-dione (84g). This dione and both the hydroxy- (84a) and acetoxy- (84f) ketones

were stable to active alumina. This is consistent with these compounds having the all-chair 5β8α-skeleton which is more stable than the 5α, 8α-skeleton which either has an all chair conformation with rings A and C in close proximity or has ring B in a skewed or boat conformation.

The structure of 3β, 5-dihydroxy-5β, 8α, 10α-cholestan-6-one (84b) was assigned on the following basis. NMR and infrared spectral data showed the presence of the C(6)-ketone and C(3) axial secondary hydroxyl function. The presence of the C(5)-hydroxyl followed from mass spectral and analytical data which indicated a molecular formula of $C_{27}H_{46}O_3$. Acetylation gave 6-oxo-5β, 8α, 10α-cholestane-3β, 5-diol 3-acetate (84j) which exhibited a proton resonance at δ 3.3ppm which disappeared upon shaking with D_2O. No signal corresponding to a CHOH moiety was observed. This confirms the presence of the 5β-hydroxyl function in the ketone (84b). The axial nature of the C(3)-acetate function was indicated by the muliplet acetate band in the infrared spectrum[91].

Reduction of the diol-ketone (84b) with lithium aluminium hydride gave 5β, 8α, 10α-cholestane-3β, 5, 6α-triol (84c) and acetylation produced 5β, 8α, 10α-cholestan-3β, 5, 6α-triol

3,6-diacetate (84k). Both compounds exhibit equatorial proton signals (δ 4.23($W_{h/2}$ 9Hz) and 3.57($W_{h/2}$ 6Hz) in the triol; δ5.29($W_{h/2}$ 8Hz) and 4.73($W_{h/2}$ 4Hz) in the diacetate). This means that the C(3) and C(6) functions are axial and this fixes the stereochemistry of these derivatives as 5β, 8α, 6α (ref. discussion on the 5-deoxy-analogues P, 57). The C(3)- and C(6)- proton signals were assigned by comparison of the 6-oxo (84b, 84j) and the 6-oxy (84c, 84k) compounds in the same manner as for the 5-deoxy-derivatives (84i and 84b). The C(6)- proton occurs upfield of the C(3) signal and this difference in chemical shift is more marked than in the 5-deoxy analogues. (Table 5). The assignments of these proton signals are in accord with the relative half-band widths - the

TABLE 5

5β8α10α-cholestane derivatives	C(3)H	C(6)H	$\Delta\delta$
-3β 5β 6α-triol (84c)	4.23	3.57	0.66
-3β, 6α-diol (84i)	4.17	3.72	0.45
-3β, 5β, 6α-triol 3,6 diacetate. (84k)	5.29	4.73	0.56
-3β, 6α-diol diacetate (84h)	5.08	4.83	0.25

signal of the C(6) proton being sharper as a consequence of having fewer vicinal couplings. This difference is less

marked in the 5-deoxy-analogues where there is there is an addition coupling of the C(6)-proton; i. e. to the C(5) proton.

A feature of the NMR spectrum of the diol-ketone (84b) and its acetoxy-derivative (84j) is a one proton quartet at ca δ3. 3ppm with observed coupling constants of 11c/s and 14c/s.* This signal is assigned to the C(7)-β-proton and its downfield position relative to the C(7)-α-proton can be attributed to the 1, 3 diaxial influence of the C(5)-hydroxyl as well as that of the adjacent keto function. In the 5-deoxy analogues (84a, 84f) the absence of this deshielding influence at C(5) means that this signal is obscured in the methylene envelope. The estimated coupling constants are consistent with those expected for $J_{7\beta H, 7\alpha H}$(geminal, 14c/s)[134] and

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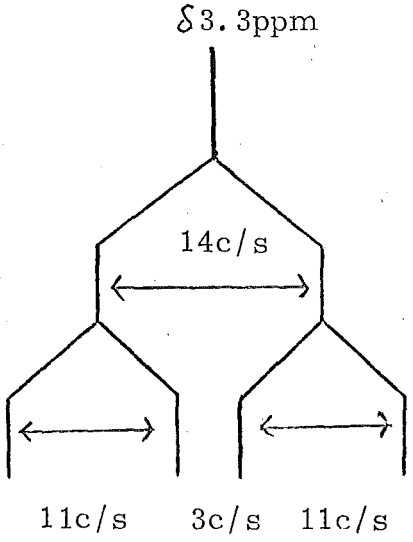

$J_{7\beta H, 8\alpha H}$ (vicinal coupling, dihedral angle 180°, 11c/s)[135]. Oxidation of the diol-ketone (84b) with Jones reagent gave 5-hydroxy-5β, 8α, 10α-cholestan-3, 6-dione (84l) which exhibits a more complex pattern at about δ 3. 3ppm. This multiplet corresponds to two protons and is assigned to the C(2) and C(7) β-protons; the chemical environment of these protons is almost identical.

The reductions of 3β, 5-dihydroxy- and 3β-hydroxy-5β, 8α, 10α-cholestan-6-ones (84b, 84a) in each case produced a C(6)-axial hydroxyl; this was of great assistance in that it immediately limited the number of possible structures.* This result parallels that of complex metal hydide reductions in the natural series where a ketone function γ to an axial angular methyl preferentially produces the axial alcohol. In particular natural 6-keto-steroids give the C(6)β-alcohols in 75-100% yields with lithium aluminium hydride[136-8] and 90-100% yields with sodium borohydride[138-41].

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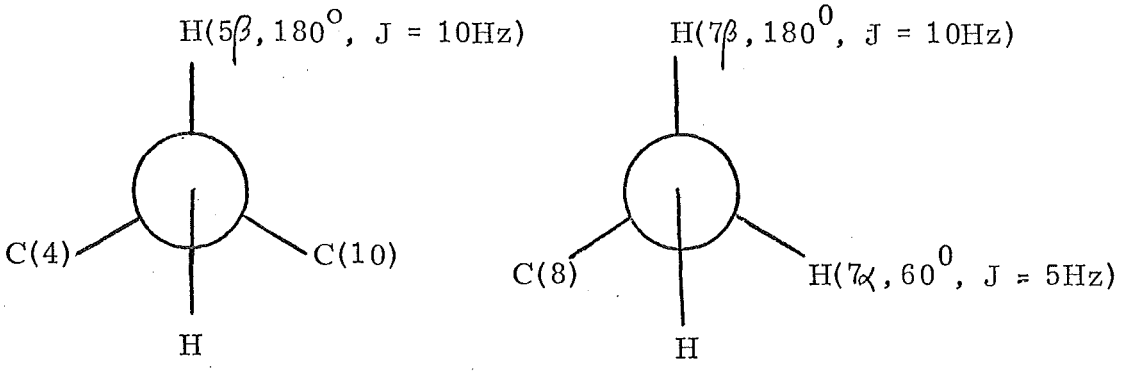
*Ref. P. 57 ; few of the 5ξ, 8ξ, 6ξ, 10α isomers have both the C(3) and C(6) hydroxyl functions in an axial configuration.

Identification of the major 5-deoxy-diol product (84e; Fig. 23) followed from oxidation of this diol with Jones reagent or chromium trioxide pyridine to 5β, 8α, 10α-cholestane-3, 6-dione (84g) identical to a sample prepared from 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a). Since this diol was not identical to 5β, 8α, 10α-cholestane-3β, 6α-diol (84i) then it is clearly the C(6)-epimer (84e). Spectral and analytical data were in accord with this formulation. In particular the NMR spectrum exhibits CHOH signals corresponding to axial (C(3)β) and equatorial (C(6)β) hydroxyl functions. The relative chemical shifts of the $C^{19}H_3$ groups in the diols (84e, 84i) agrees with that expected by analogy with the natural series - the 6α-hydroxyl is 1, 3-syn to this methyl and deshields it by 0.20ppm relative to the 6β-hydroxyl which is 1, 3-anti to the methyl. In the natural series inversion of C(6) hydroxyl from a position 1, 3-anti- to the methyl to a 1, 3-syn relationship causes a 0.23ppm downfield shift[87].

Acetylation of the diol (84e) under mild conditions gave 5β, 8α, 10α-cholestane-3β, 6β-diol diacetate (84m; 66%) and 5β, 8α, 10α-cholestane-3β, 6β-diol 6-acetate (85n; 33%). The NMR spectrum of the mono-acetate exhibited a one proton sextet at δ 4.61ppm consistent with coupling constants of

10c/s, 10c/s, and 5c/s; and a 'sharp', ($W_{h/2}$ 8Hz), CHOH signal at δ4.09. Dihedral angles for the C(6) α-proton are shown in Fig. 36; the coupling constants for theCHOAc resonance



-Fig. 36-

are in accord with these dihedral angles. The simple Karplus equation[135] implies J=2.5 Hz when ϕ = 60° but when one of the protons involved is geminal to an equatorial oxy function then J≈5Hz[142,143]. Oxidation of the monoacetate (84n) with chromium trioxide-pyridine gave 3-oxo-5β,8α,10α-cholestan-6β-yl acetate (84o).

Mass spectral and analytical data for the minor diol product (85a; Fig. 23; P.43) indicated a molecular formula of $C_{27}H_{46}O_2$. The infrared spectrum exhibits hydroxyl bands but no carbonyl absorbtions. This product was therefore assigned as a 5ξ,8ξ,10α-cholestane-3β,6ξ-diol. The NMR spectrum exhibits a 'two proton' signal at ca δ4.08ppm which

appears to be a combination of a broad and a sharp signal; i. e. one hydroxyl group is axial (corresponding to a sharp CHOH signal) whilst the other is either equatorial or is in a ring with a boat conformation. Mild acetylation of diol (85a) afforded 5α, 10α-cholestane-3β, 6α-diol 6-acetate (85e, 33%) and 5α, 10α-cholestane-3β, 6α-diol diacetate (85f, 66%).* Spectral data indicates the presence of an axial hydroxyl (3375cm^{-1}; δ 4.02ppm, $W_{h/2}$ 9Hz) and a non-axial** acetoxyl (ν 1735, 1250 (singlet)cm^{-1}; δ 5.55ppm, sextet, J≈5Hz) in the monoacetate (85e). The diacetate (85f) exhibits a multiplet acetate band[91] in the infrared spectrum and methine signals at δ 5.00 ($W_{h/2}$ 7Hz) and 5.13 ("broad") ppm. This data confirms the above observation on the configurations of the hydroxy-functions in the diol (85a). Chromium trioxide-pyridine oxidation of the mono-acetate (85e) gave 3-oxo-5α, 10α-cholestan-6α-yl acetate (85g); spectral and analytical data

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*To simplify the presentation the actual structures of the derivatives of diol (85a) are assumed in their nomenclature in the text and only the diol is referred to in more general terms.

**Non-axial: function is either in a ring with a boat conformation or it is equatorial in a ring with a chair conformation.

was in accord with this formulation. Oxidation of the diol (85a) with Jones reagent or chromium-trioxide-pyridine yielded 5α, 10α-cholestane-3, 6-dione (85h). Neither the keto-acetate (85g) nor the diketone showed spectral evidence of a hydroxyl function consistent with the 5-deoxy- structure assigned to the diol (85a) and its derivatives. The dione (85h) was stable on active alumina.

The configurational assignment of the above series of compounds (85a, 85e, 85f, 85g, 85h) was made on the following basis. Diol (85a) is not equivalent to either of the previously characterized 5β 8α-diols (84e, 84i); therefore the series has the 5α 8α 10α-, 5α 8β 10α- or the 5β 8β 10α- skeleton. The 5α 8β 6β-diol (85i) has two axial hydroxyl functions inconsistent with the observed data on diol (85a) and its acetoxy derivatives (85e, 85f). The remaining five possible isomers of diol (85a) i.e. 5α 8β 6α, 5β 8β 6ξ and 5α 8α 6ξ would all give rise to the observed "sharp plus broad" two proton signal at δ 4.08ppm.

Oxidation of diol (85a) with chromium trioxide-pyridine or Jones reagent produced 5α, 8β, 10α-cholestane-3, 6-dione (85h) and this product is stable on active alumina. These observations are indicative of a stable C(5) configuration.

The 5β, 8β, 10α- skeleton has ring B in a boat configuration and would be expected to epimerize to the 5α,8β, 10α-isomer with the all-chair conformation. Similarly the 5α, 8α, 10α-isomer should epimerize to the more stable 5β, 8α, 10α-isomer; as noted earlier the 5α, 8α, 10α- all chair conformer contains substantial steric interference between the C(9)-C(11) bond and ring A and may prefer to exist in a conformation with ring B skewed or boat to relieve this. Whatever the preferred conformation of this isomer is, it is clearly less stable than the 5β, 8α, 10α-isomer where rings A and C are less proximate. The 5α, 8β, 10α- isomer would not be expected to epimerize under either the acid (Jones oxidation) or base (Al_2O_3) conditions; i. e. the above observation on the stability of dione (85h) tends to suggest a 5α, 8β, 10α-skeleton for the series under discussion.

This series of compounds exhibit a $C^{18}H_3$ signal between δ 0. 64-0. 67ppm; i. e. the chemical shift of this methyl is relatively insensitive to variation of the C(6)-substituent. The chemical shifts of angular methyl groups have been reported for a number of stereoisomeric steroid skeletons[34, 87, 115] (Table 23 P. 122). The $C^{18}H_3$ shift in 5ξ-cholestane is

0.64ppm* and structural variation at C(14), C(8) or C(9) causes a marked deshielding of this methyl relative to its "natural shift", in particular this methyl is ca 0.15ppm further downfield in the 8α-isomer (V, Table 23). Variation of the C(5) configuration has a negligible influence (I vs. IV in Table 23) and from the discussion on the Δ^7-olefins (Table 2) variation about the C(5)-C(10) bond has little effect on this shift. Additive shift data for the natural series[87] and the 8α,10α-series** show a relative insensitivity to variations in C(3) and C(6) substitution. Therefore the $C^{18}H_3$ chemical shift in the series under discussion is consistent with the 5β,8β- and 5α 8β- structures and convincingly excludes the 5α, 8α- structure.

The $C^{19}H_3$ signal occurs at δ 1.02ppm in the mono-acetate (85e) and at δ1.28ppm in the acetoxy-ketone (85g). As far as the chemical environment of this methyl is concerned the transformation (3β-OH→ 3-oxo) in the 8β,10α-steroids is equivalent to the transformation (3α-OH →3 oxo) in 5α-natural steroids. (Fig. 37). In the natural isomers the

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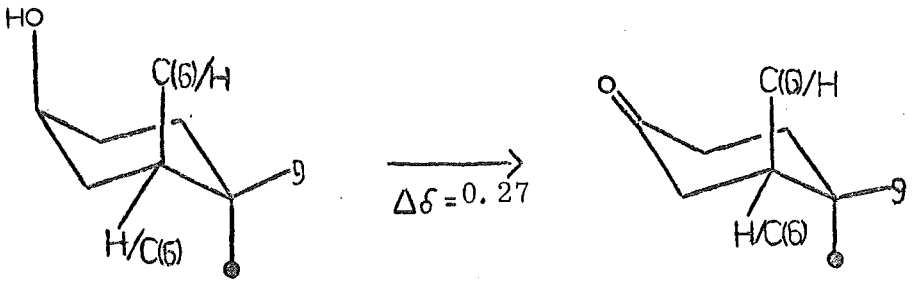
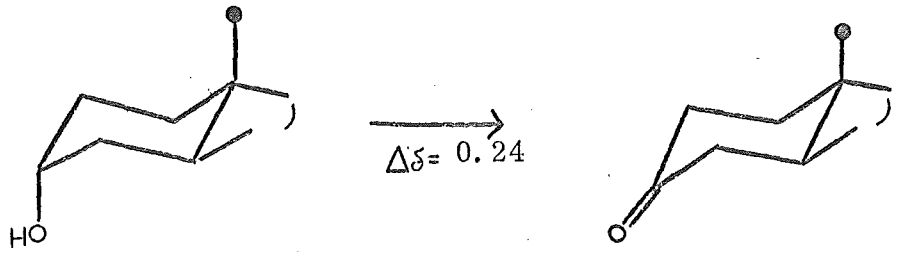
*Data from Table 23 combined with "Zurcher value" for $17\beta\ C_8H_{17}$

**Ref. Table 18, P. 112.



5ξ, 10α:

3β-hydroxyl (85e) C(3) ketone (85g)

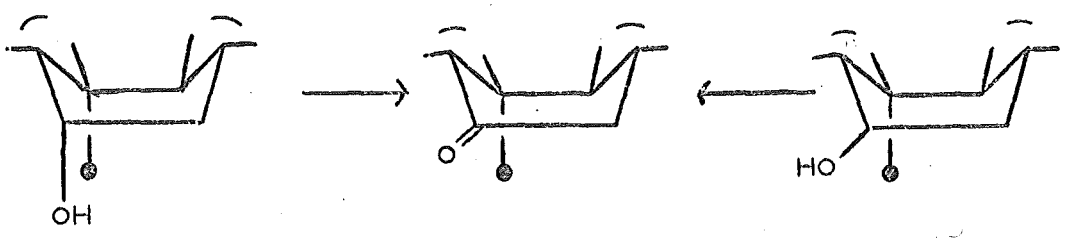


5α: 3-hydroxyl 5α: 3-ketone

-Fig. 37-

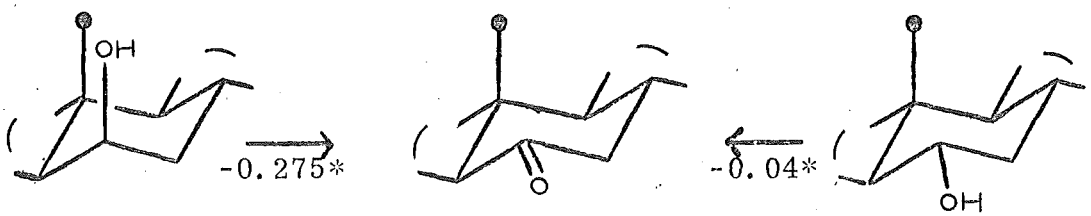
effect of this is to deshield this methyl by ca 0.24ppm[87]; the observed effect in these unnatural analogues (ie. $\Delta\delta$(3 ketone)-—(3β-hydroxy) = 0.27ppm) is, as expected, comparable. Oxidation of diol (85a) to dione (85h) causes a downfield shift of δ0.35ppm for the $C^{19}H_3$ signal. From the preceding discussion it is known that ca 0.24-0.27ppm of this change is

Fig. 38(a) 5β, 10α-skeleton; ring B



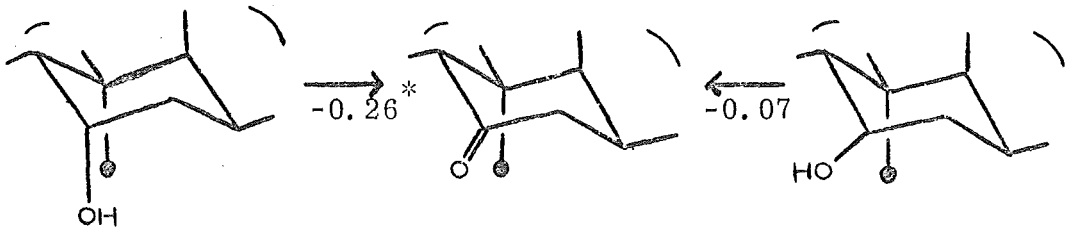
6α-hydroxyl 6-ketone 6β-hydroxyl

Fig. 38(b) 5α-skeleton; ring B



6β-hydroxyl (+0.225)** 6-ketone (-0.05)** 6α-hydroxyl (0.01)**

Fig. 38(c) 5β, 8α, 10α-skeleton; ringB



***(84i); δ 1.11 (84a); δ 0.85 (84e) δ 0.92

*Incremental shift for $C^{19}H_3$ upon substituent change at C(6);

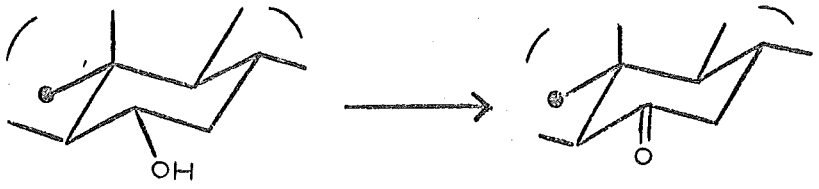
**Additive shift value for relevant substituent;

***Absolute shift values for $C^{19}H_3$.

accounted for by the alteration at C(3) so it is estimated that the oxidation of the C(6)-hydroxyl causes this methyl to shift ca 0.08-0.11ppm. In the 5β, 8β-skeleton the relationship of the $C^{19}H_3$ group to the C(6)-hydroxyl is shown in Fig. 38a. It is comparable to the situations in the 5α-natural (Fig 38b) and 5β, 8α, 10α- (Fig 38c) 3,6-diols. From this analogy the oxidation of the C(6) hydroxyl in the 5β8β-isomer should result in a ca .0.27ppm or a 0.04-0.07ppm upfield shift in the C(10) methyl resonance position. This is inconsistent with the "observed" shift (above) of ca 0.08 ppm downfield for the $C^{19}H_3$ chemical shift with variation of the C(6)- function. This provides further evidence against the 5β, 8β, 6ξ-structure for diol (85a).

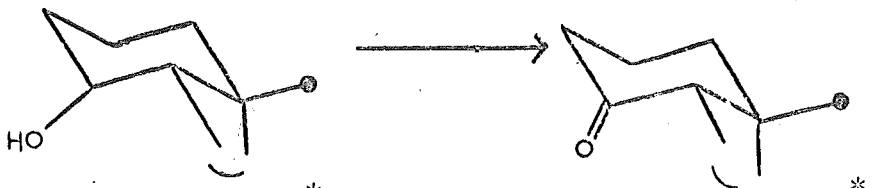
This shift data is, however, consistent with the remaining structural possibility, (the 5α, 8β, 6α-isomer), where the substituent variation at C(6) is comparable to the oxidation of 4β-hydroxy-5α-natural steroids (Ref. Fig. 39). Such an analogy would suggest that oxidation of the C(6)-hydroxyl should result in a ca 0.14ppm downfield shift for the $C^{19}H_3$ signal; in fact a downfield shift of 0.08ppm was observed. However this is a better fit than was obtained for the structure discussed in the previous paragraph where this

5α, 10α-isomer; ring B



6β-hydroxyl 6-ketone

5β-isomer; ring A



4β-hydroxyl (0.04)* 4-ketone (0.18)*

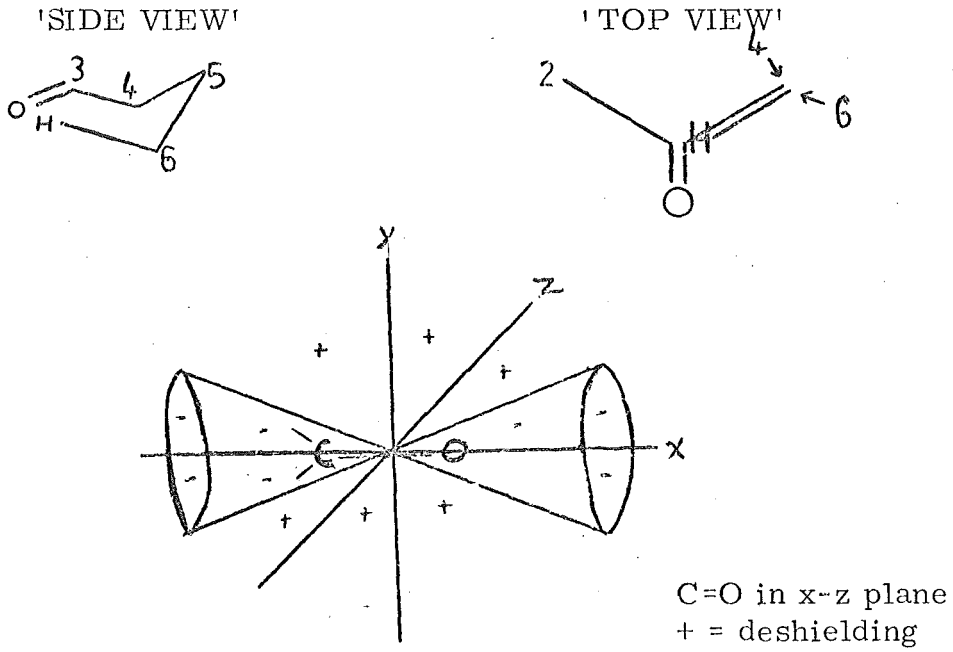
Fig. 39

*Additive shift values[87, 144]

oxidation would cause a shift in the opposite direction.

Finally the C(6) methine signals provide strong support for the 5α, 8β, 10α, 6α-structure for this series. The shape of the methine resonance ("two proton") in the diol (85a) suggests that the broad component of this signal is centred downfield of the sharp component. The distinction is clearer in the diacetate (85f) where the axial C(6)-proton occurs at δ5.22ppm

compared to the equatorial C(3)-proton at δ 5.00ppm. This abnormally deshielded position* for the axial C(6) proton can be attributed to the proximity of the C(3)-hydroxyl in this structure. It is the proximity of the 3β-hydroxyl with the C(6) in 5α, 10α-structures which permits the formation of the derivatives (71a, b) referred to on P. 30. Oxidation of the mono-acetate (85e) to the acetoxy-ketone (85g) results in a shift of the C(6)-proton resonance from δ5.5ppm to δ4.6ppm. In the ketone (85g) the C(6)- proton is in close proximity in the shielding region[147, 148] of the C(3)-ketone (Fig. 40). The



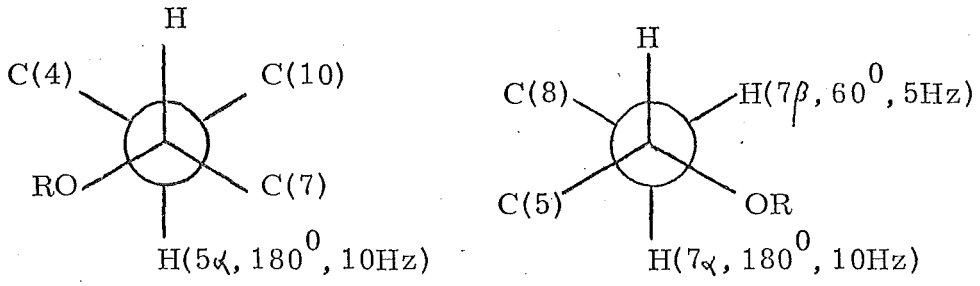
C=O in x-z plane
+ = deshielding

-Fig. 40-

*Axial protons are generally upfield of equatorial protons[145, 146].

large upfield shift ($\Delta\delta$=0.9ppm) is a consequence of replacing a large deshielding influence (C(3)-hydroxyl) with a large shielding influence (C(3)-ketone).

On the basis of the foregoing discussion the diol (85a) was assigned as 5α, 10α-cholestane-3β, 6α-diol (85c) and its derivatives assigned as given in the text (Pp. 65-7). In this structure the dihedral angles for the C(6)-proton are shown in Fig. 41. The expected coupling constants for



-Fig. 41-

this proton are therefore ca 10Hz, 10Hz, 5Hz[135, 142] (Ref. P. 65). In general the signal of the C(6) proton was broad and unresolved, (in the C(6)-hydroxy and C(6)-acetoxy derivatives in this series), but in the diacetate (85f) it appeared to be a sextet with peak ratios 1:1:2:2:1:1 consistent with the expected coupling constants.

The identity of 5β, 10α-cholest-7-en-3β, 5, 6β-triol (70h) followed from allylic oxidation to 5β, 10α-cholest-7-en-6-one (70f)

and its non-identity to 5β, 10α-cholest-7-en-3β, 5, 6α-triol (70d). An inspection of Dreiding models showed the dihedral angle between the C(6) α-proton and the C(7) proton is 80-90° and accordingly no coupling was observed. The assignments of these epimeric triols are in accord with the observed chemical shifts of the $C^{19}H_3$ group; the 6α-epimer (70d) with a 1, 3-syn relationship between the $C^{19}H_3$ and C(6)-hydroxyl, exhibits the $C^{19}H_3$ signal at δ 1.13ppm. The 6β-epimer (70h) has a 1, 3-anti relationship of methyl and hydroxyl and exhibits the C(10) methyl signal at δ 0.97ppm. In the natural series a 6β-hydroxyl (1, 3 syn to the C(10)-methyl) deshields the C(10)-methyl by ca 0.23ppm* more than a 6α-hydroxyl (1, 3-anti to the methyl) does.

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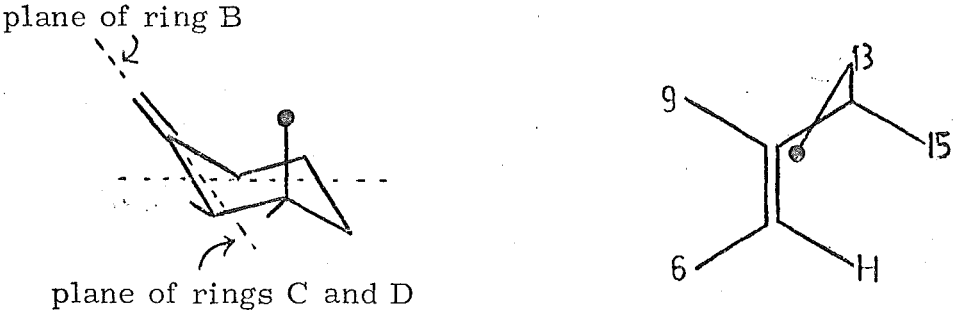
*Approximate value; difference between "additive shift values" for influence of C(6) hydroxyls on the $C^{19}H_3$ shift[87].

The reaction of 5β, 10α-cholest-7-en-3β-ol (65c) with m-chloroperbenzoic acid is slow (ca 96 hours) and produces 7α, 8α-epoxy-5β, 8α, 10α-cholestan-3β-ol (100). Spectral and analytical data is in accord with this formulation. The configuration of the epoxy function follows from the chemistry of this compound described below. This assignment is consistent with the relative hindrance to attack on the α- or β - face of the olefin (65c). Inspection of Dreiding models show that in this compound rings C and D are inclined at an angle of ca 100° to ring B with the consequence that the $C^{18}H_3$ group offers a severe steric constraint to β-face attack of the Δ^7-olefin. (Ref. Fig. 42). Some hindrance is also



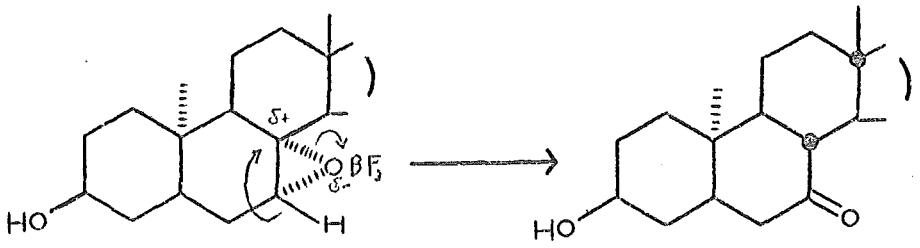
-Fig. 42-

caused by the C(5) proton and ring C. However the α-face is relatively unhindered with rings C and D clear of this face.

Also the $C^{19}H_3$ group is more removed from the olefinic bond than the $C^{18}H_3$. However this group, and the 14α-proton, offer some resistance to epoxidation from the favored α-face and this is reflected in the reaction time. Alt and Barton[149] have reported the epoxidation of 5α-ergosta-7, 22-dien-3β-ol (101, x = OH) to 7α, 8α-epoxy-5α-ergost-22-en-3β-ol (102, x = OH) in eighteen hours with monoperphthalic acid. Attack at the β face is hindered by the $C^{18}H_3$ group, as shown in Fig. 42, and by the $C^{19}H_3$ group. The faster reaction time, relative to the 10α-analogue (65c) reaction, is due to the reduced constraint on the α-face when both angular methyls are β-oriented. Mayor and Meakins[150] report titrations of 9β, 10α-ergost-7, 22-dien-3β-ol derivatives (103) with perbenzoic acid; they found that increasing hindrance on the β-face caused a reduced reaction rate and hence deduced that these derivatives epoxidize on this face. In this isomeric skeleton (9β, 10α) the $C^{18}H_3$ group is much further from the Δ^7-olefinic bond than in the natural- and 10α-isomeric systems discussed above.

The BF_3-etherate catalyzed rearrangement of 7α, 8α-epoxy-5β, 8α, 10α-cholestan-3β-ol (100) produced 3β-hydroxy-5β, 8β, 10α-cholestan-7-one (104a) in quantitative yield. Spectral and analytical data are in accord with the above formulation.

The alternative 8α-configuration for this ketone was eliminated on the basis of the C(10)-angular methyl ($C^{19}H_3$) chemical shift. For the 8α-isomer of (104a) the position of this resonance is estimated as shown in Table 6. The NMR spectrum of the ketone (104a) exhibits angular methyl resonances at δ0.68 and δ0.84ppm and this is clearly incompatible with the 8α-configuration. On this basis the ketone (104a) was assigned the 8β-configuration and the epoxide (100) as 7α, 8α; (Fig. 43).



-Fig. 43-

The position of the $C^{19}H_3$ signal in the 8β-isomer (104a) can be estimated by direct comparison with a natural analogue (Fig. 44). This resonance occurs at δ0.66ppm in cholestan-7-one (105)* As previously noted variations in the

*Calculated value from Zurcher Data[87].

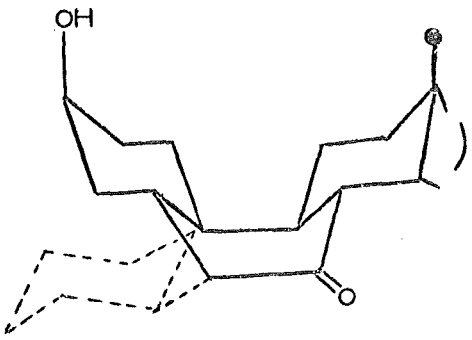
TABLE 6

Base value[a]	8α, 10α-cholestane	0.91[a]
Incremental shifts	3β-hydroxyl	+0.00[b]
	7-keto-	+0.22-0.27[c]
Estimated shift of C(10)-methyl in 8α -isomer of (104a)		(1.13-1.18)ppm

(a) Ref. Pp.105-7 this thesis.

(b) The 3β-hydroxyl is 1,4-anti with respect to the C(10)-methyl; this is the steric relationship of a 3α-hydroxyl to this methyl in natural-5α-derivatives and the additive value for this is +0.00[87].

(c)A ketone function γ to an axial methyl function (in a chair ring) deshields that methyl by ca 0.22-0.27ppm. Representative values for such an influence are +(0.22-0.24)ppm for the deshielding of the C(10) methyl by the C(3) keto function in A/B-trans steroids[34, 87] and +(0.27)ppm for the influence of the 7-keto function on this methyl in 5α-natural steroids[87].



104,

ring A of 5α-natural analogue (105)

-Fig. 44-

orientation of ring A have little influence on the C(13)-methyl chemical shift because of the distance between ring A and this methyl. For the same reason the 3β-hydroxyl group is of little importance in this comparison*. The $C^{18}H_3$ signal occurs at δ0.68ppm in the ketone (104a). Acetylation of the hydroxy ketone (104a) gave 7-oxo-5β,10α-cholestan-3β-yl-acetate.

Oxidation of the hydroxy-ketone (104a) with Jones reagent gave 5β,10α-cholestane-3,7-dione (104c); as for the hydroxy-ketone (104a) the 8α-configuration for this compound

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*This estimate is qualitative only, and intended simply to show the compatability of the assigned structure with the NMR data.

is ruled out on the basis of the $C^{19}H_3$ signal in the NMR spectrum. The hydroxy-ketone (104a) was recovered unchanged after adsorption on and elution from active alumina. Inspection of Dreiding models show that the 5β, 8α, 10α-skeleton has an all chair conformation whilst the 5β, 8β, 10α-skeleton has a boat ring B, yet the 8β-7-ketones (104a, 104c) are stable to acid (Jones reagent) and base (Al_2O_3). It is probable that this can be attributed to preferred enolization of the 8β-7-ketones (104a, c) towards C(6) rather than C(8). In the formation of the enol form (106) from the 8β-7-ketone the C(13)-methyl moves toward ring B and this clash makes enolization towards C(8) prohibitive.

In the natural series the reaction of 5α, 6α-epoxides with boron trifluoride-etherate in dimethyl formamide has been reported to produce the 5α-hydroxyl-6β-formoxy-derivatives[151]. In these compounds the nucleophilic attack of the solvent at C(6) takes precedence over internal rearrangement. However reaction of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100) under these conditions gave exclusively the hydroxy-ketone (104a); i.e. the 'rearrangement product'. The absence of products arising from nucleophilic attack by the solvent may be attributed to the steric constraint which

the $C^{18}H_3$ group places upon β-face attack at C(7) (this is a similar effect to that observed in the Δ^7-olefin (65c)*). Treatment of the epoxide (100) with perchloric acid in aqueous acetone likewise produces the hydroxy-ketone (104a) and no products of nucleophilic attack. Reaction of $7\alpha, 8\alpha$-epoxy-$5\beta, 8\alpha, 10\alpha$-cholestan-$3\beta$-ol(100) with formic acid gave 7-oxo-$5\beta, 10\alpha$, cholestan-3β-yl formate (104d). The infrared spectrum of this product exhibits bands which show the presence of ketone (ν 1710cm^{-1}) and formate (ν 1725, 1188cm^{-1}) functions. The formate function is confirmed by the NMR spectra which exhibits "one proton" signals at δ8.08 ($W_{h/2}$ ca 1c/s) and δ5.2 ($W_{h/2}$ 7Hz)ppm. The angular methyl chemical shifts were indicative of an 8β- rather than an 8α-configuration (ref. discussion on the 3β-hydroxy-derivative on Pp.79/80. Alkaline hydrolysis of the formate (104d) gave the hydroxy-ketone (104a), identified by NMR spectrum; acetylation gave the acetoxy-ketone (104b) identical by melting and mixed melting point to a sample produced via BF_3 rearrangement of the epoxide (100).

$7\alpha, 8\alpha$-Epoxy-derivatives in the natural series have been reported to be resistant to reductive opening with lithium aluminium hydride[152]. This was attributed to the

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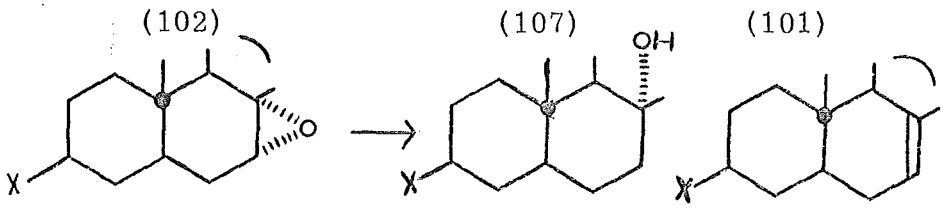
*Ref. P. 77.

large steric requirement of the reductant and the hindrance to β-face attack afforded by the angular methyls. Similarly 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100) failed to react with lithium aluminium hydride even after heating under reflux for 24hrs. in tetrahydrofuran. Although the C(10)-methyl is on the α-face in this compound the relationship of the C(13)-methyl to the epoxy function is the same as in the natural series.

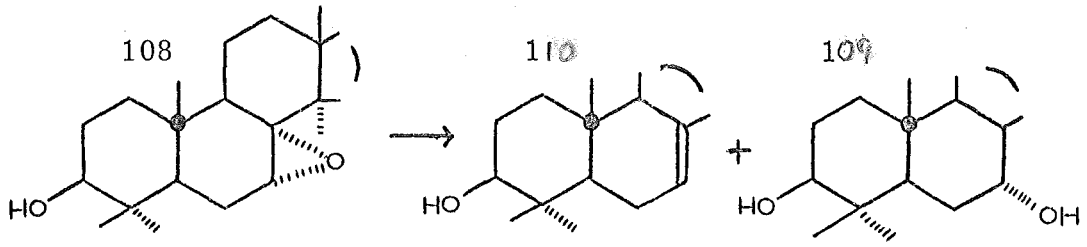
However such reductions may be effected by the use of lithium in ethylamine where the steric requirement of the reductant is much smaller. Hallsworth and Henbest[153] reported that 3-substituted-7α, 8α-epoxy-5α-ergost-22-enes (102) are reduced by this reagent to the 8α-alcohols (107) and $\Delta^{7,22}$-dienes (101), Fig. 45. The hydroxyl function in (107) was assigned as tertiary on the basis that it failed to



-Fig. 45-

acetylate under conditions that normally esterify a secondary alcohol. However Brown and Borkenhagen[154] found that 7α, 8-epoxy-5α, 8α-lanostan-3β-ol (108) was reduced with

lithium-ethylamine to the Δ^7-olefin (109, 25%) and the 3β, 7α-diol (110, 43%), Fig. 46. They repeated the previously



-Fig. 46-

reported reduction of 7α, 8α-epoxy-5α, 8α-ergost-22-en-3β-ol (102, x = OH) and found that the diol product* (111a) upon treatment with acetic anhydride in pyridine for 18 hrs. gave mainly 5α-ergost-22-ene-3β, 7α-diol 3-acetate (111b) but also the C(3), C(7)-diacetate (111c). The C(7)-hydroxyl function in the diol (111a) was assigned by observation of the associated CHOH signal in the NMR spectrum. It was, in fact, the unexpected resistance of this hydroxyl towards acetylation which had misled the previous workers.

Reduction of 7α, 8-epoxy-5α, 8α, 10α-cholestan-3β-ol (100) with lithium-ethylamine followed by acetylation** of the crude product gave 5β, 8α, 10α-cholestane-3β, 7α-diol

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*Identical by MPt, $[\alpha]_D$ to that reported as (107a)[153]

**Ac_2O/pyridine overnight at room temperature; heat on steam bath for two hours.

diacetate (112a, 50%) and 5β, 8α, 10α-cholestane-3β, 8α-diol 3-acetate (113a, 18%). The remainder of the product (ca 12%) consisted of a non-polar mixture of compounds which gave no signals in the olefinic region of the NMR spectrum and gave a negative test to tetranitromethane; the mixture was not further investigated.

The NMR spectrum of the mono-acetate (113a) exhibits a methyl signal at δ 2.07ppm and an equatorial methine signal at δ 5.03ppm ($W_{h/2}$ 8Hz). There was no signal corresponding to a CHOH moiety but when the sample was shaken with D_2O an HOD peak appeared at δ 4.57ppm. Elemental analysis indicated a molecular formula of $C_{29}H_{50}O_3$ and the infrared spectrum showed the presence of acetoxy- and hydroxy- functions. The above data shows the compound to contain a secondary axial acetate function and a tertiary hydroxyl function. Angular methyl resonances were observed in the NMR spectrum at δ 0.82 and 1.23ppm, where the downfield signal clearly represents the methyl which is 1,3-diaxially related to the C(8)-hydroxyl group. Protons or methyl groups 1,3-syn-diaxial to hydroxyl functions are strongly deshielded[87, 156, 155]. If the C(8) hydroxyl in monoacetate (113a) has the α-configuration then the downfield methyl is $C^{19}H_3$ but if this hydroxyl has the β-configuration then the signal at δ 1.23ppm is that of $C^{18}H_3$.

Table 7 gives representative 'additive shift values' for hydroxyl functions 1, 3-diaxial with respect to methyl groups.

TABLE 7

Additive shift values in 5α- and 5β- steroids[87]

C(5)	Hydroxyl position	Affected Methyl	Additive Shift Value(b)
5α	2β	$C^{19}H_3$	+ 0.25
5α	4β	$C^{19}H_3$	+ 0.27
5α	6β	$C^{19}H_3$	+ 0.225
5β	6β	$C^{19}H_3$	+ 0.19
5ε	8β	$C^{19}H_3$	+ 0.18
5ε	11β	$C^{19}H_3$	+ 0.26
5ε	8β	$C^{18}H_3$	+ 0.18 (0.26)[a]
5ε	11β	$C^{18}H_3$	0.24

(a) K. Tori and E. Kondo, Tetrahedron Letters, 1963, 10, 645

(b) in ppm; positive value implies a deshielding influence.

Assignment of the C(8) configuration in the mono-acetate (113a) follows from a consideration of the angular methyl chemical shifts. Firstly, consider the possibility that this compound is 5β, 10α-cholestane-3β, 8β-diol-3-acetate. The chemical shift of the $C^{18}H_3$ group in 5ε-cholestane is

δ0.64ppm[87]. Previously it was noted for 5ξ,10ξ-Δ^7-derivatives (Pp. 24-6) that the 5β,10α- and 5ξ,10β- derivatives showed similar $C^{18}H_3$ methyl shifts. Also the saturated 5α, 8β, 10α-derivatives discussed on Pp.65-7 show a $C^{18}H_3$ signal at ca δ 0.64-0.67ppm. Hence it may be reasonably assumed that variation of the C(5)-C(10) stereochemistry from 5ξ, 10β- (natural) to 5β, 10α has little or no influence on the $C^{18}H_3$ chemical shift; i.e. a value of δ 0.64ppm is estimated for this shift in 5β, 10α-cholestane (115a).

On similar grounds the influence of the 3β-acetoxy function on this shift may be ignored. The effect of the 8β-hydroxyl function is assumed to be +(0.18-0.27)ppm, ref. Table 7. Therefore the $C^{18}H_3$ signal in 5β, 10α-cholestane-3β, 8β-diol 3-acetate would be expected to appear at ca δ (0.82-0.91)ppm (Table 8). This is incompatible with the observed value of

TABLE 8

	$\delta(C^{18}H_3)$ppm
5β, 10α-cholestane	0.64
3β-acetate	-
8β-hydroxyl	+ 0.18-0.27
Total	0.82-091

δ1.23ppm for the methyl "1,3-diaxial to the tertiary hydroxyl" (P.86).

For the 8α-isomer (113a) the estimated value of the $C^{19}H_3$ chemical shift is δ(1.11-1.20)ppm, Table 9; this compares far better with the observed value of δ1.23ppm. Similarly

TABLE 9

$C^{19}H_3$ chemical shift in 5β, 8α, 10α-cholestane-3β, 8-diol 3-acetate.

		$\delta(C^{19}H_3)$
5β, 8α, 10α-cholestane	δ	0.91 (a)
3β-acetate	$\Delta\delta$	+ 0.02 (b)
8α-hydroxyl	$\Delta\delta$	+ 0.18-0.27 (c)

(a) Ref P.107 .; (b) 'additive shift value' for a 3 -acetate function in a '5α10β'-steroid; (c) Table 8.

the chemical shift of the $C^{18}H_3$ group in 5β,8α, 10α-cholestane-3β, 8-diol 3-acetate (113a) can be estimated (Table 10). Again the estimated (ca 0.78-0.82ppm) and observed values (0.82ppm) are in good accord. Therefore, without any a priori assumption regarding the configuration of the epoxide from which it was formed, the mono-acetate (113a) may be assigned as 5β, 8α, 10α-cholestane-3β, 8-diol 3-acetate.

This provides additional, independent, confirmation of the configurational assignment of the epoxide (100) as 7α, 8α.

TABLE 10

8α, 10α-androstane	δ 0.84ppm[34]	
17β-C_8H_{17}	Δδ -0.05ppm	(a)
3β-acetate	(negligible)*	(b)
8α-hydroxyl	Δδ -(0.01) to (+ 0.025)	(c)
TOTAL (approx).	δ(0.78-0.815)ppm	

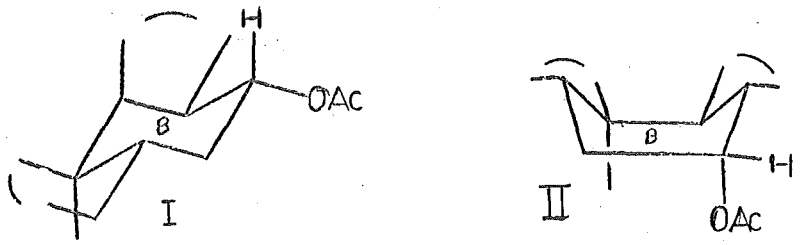
(a) the 'natural' value*; (b) the distance between the methyl and this function make its influence of little importance; (c) from representative values of analogous situations (i.e. hydroxyl 1, 3 anti-related to an axial methyl) in the natural steroids (ref. Table 11).

TABLE 11

influence of hydroxyl 1, 3-anti to axial methyl[87]

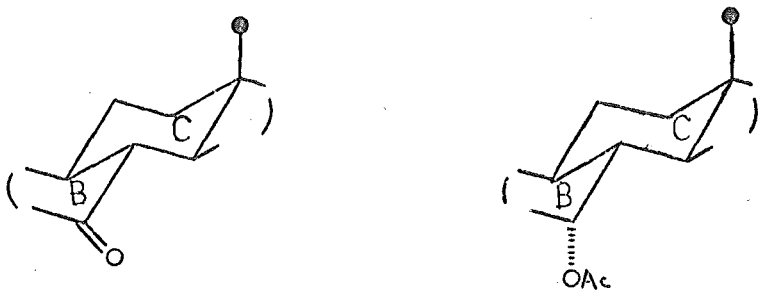
Hydroxyl	Methyl	"Additive Shift" (ppm)
4αOH	$C^{19}H_3$	+0.01
6αOH	$C^{19}H_3$	-0.01
11αOH	$C^{18}H_3$	+0.025

Assignment of the major product (112a) as a 3, 7 diacetate follows from infrared (ν1735, 1230cm^{-1}) and NMR (δ2.00, 2.06ppm) spectral data. Methine resonances were observed at δ 5.00 ($W_{h/2}$ 7Hz) and 5.23ppm (unresolved multiplet). The C(3)-α proton is equatorial, (whatever the c/8 configuration is), so the multiplet signal is therefore that of the C(7)-proton. This is consistent with either the 7α, 8α- (I) or 7α, 8β (II) structure. (Fig. 47).



-Fig. 47-

However the 8β-isomer (II) may be excluded on the basis of the $C^{18}H_3$ chemical shift. The relationship of the C(7)-substituent to this methyl is comparable to that in the natural series (Fig. 48). From additive shift values in the natural



-Fig. 48-

series a C(7)-α-acetate function shields the $C^{18}H_3$ group by 0.01ppm relative to a C(7) ketone function. 3β-Hydroxy 5β,10α-cholestan-7-one (104a) exhibits the $C^{18}H_3$ signal at δ 0.69ppm, therefore the estimated value in the 8β-isomer of diacetate (112a) is δ 0.68ppm, compared to an observed value of δ 0.83ppm. There is no suitable analogy with which to estimate the $C^{19}H_3$ shift for this isomer. Similarly there is no natural analogue from which to estimate the effect of the 7α-acetate group on the $C^{18}H_3$ shift in the 8α-isomer (I, Fig. 52). However it is possible to estimate the chemical shift of the $C^{19}H_3$ group in this isomer. (Table 12). The "calculated" value (0.97-0.98ppm) compared well with the observed value of 0.97ppm. Therefore on the basis of the

TABLE 12

C(10)-methyl shift in 5β, 8α, 10α-cholestan-3β, 7α-diol diacetate

8α, 10α-cholestane	δ 0.91ppm[a]
7α-acetate	$\Delta\delta$ +0.04-0.05[b] ppm
3β-acetate	$\Delta\delta$ +0.97-0.98[c] ppm
TOTAL (approx)	δ 0.97-0.98ppm

(a) P. 107 ; (b) "additive shift values" for influence of 3β- and 7β- acetate functions on the C(10)-methyl in 5α-natural steroids[87]. (c) The value for the 3α-acetate in 5α-natural series[87].

angular methyl chemical shift data the diacetate was assigned as 5β, 8α, 10α-cholestan-3β, 7α-diol diacetate (112a).

The reduction of the 7α, 8α-epoxide (100) with lithium-ethylamine gave a markedly different result than those reported in the 'natural steroids' (Fig. 49)[152,153]. The reductive cleavage of an epoxide ring to an alcohol has been proposed to proceed via a two electron addition[157] followed by protonation of the resultant dianion (Fig. 50). For the "natural" 7α, 8α-epoxide this reaction may occur as shown in (Fig. 51). The 8-oxygenated intermediate (I) has ring B in a boat

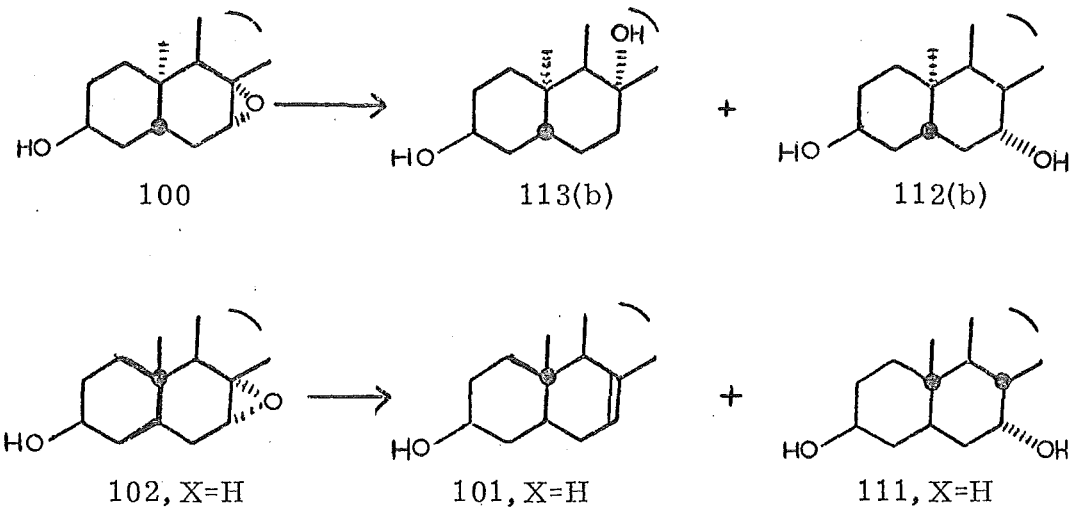


Fig. 49

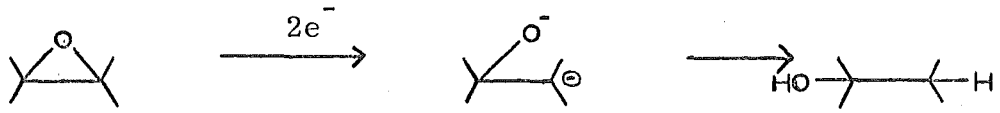


Fig. 50

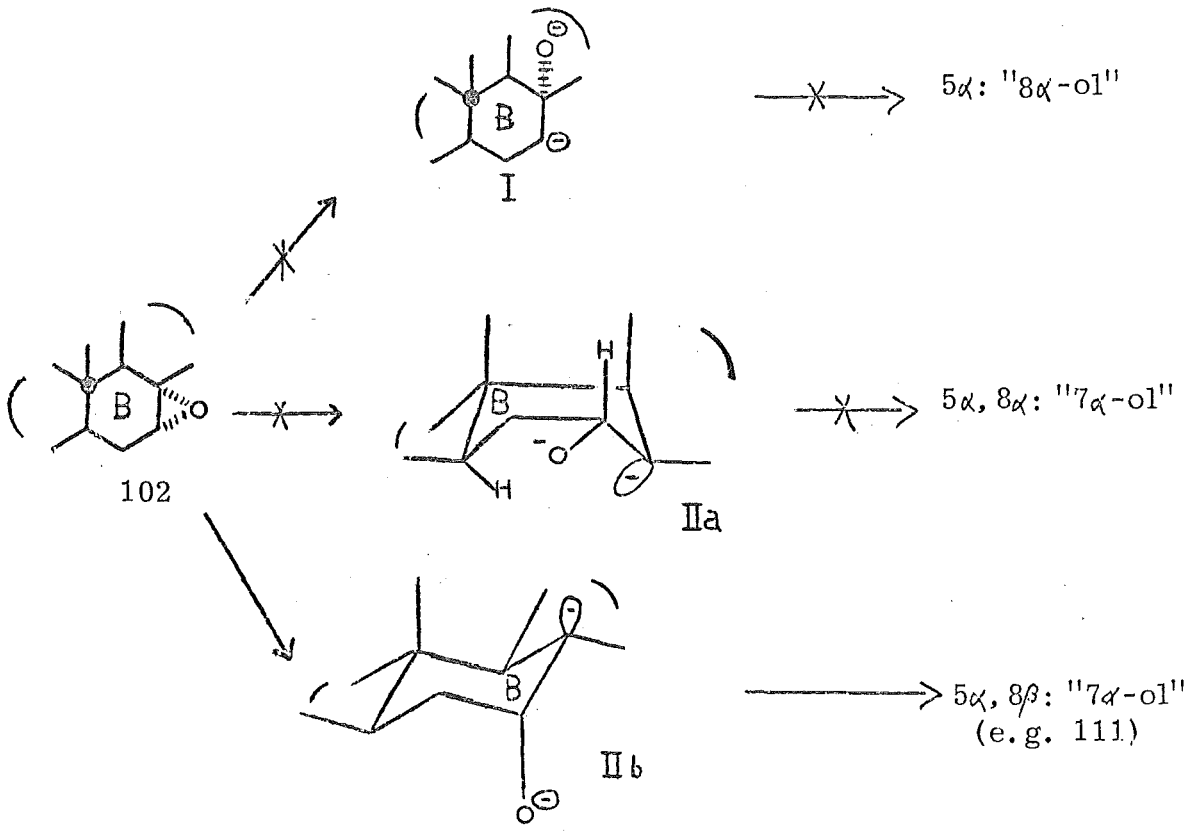


Fig. 51

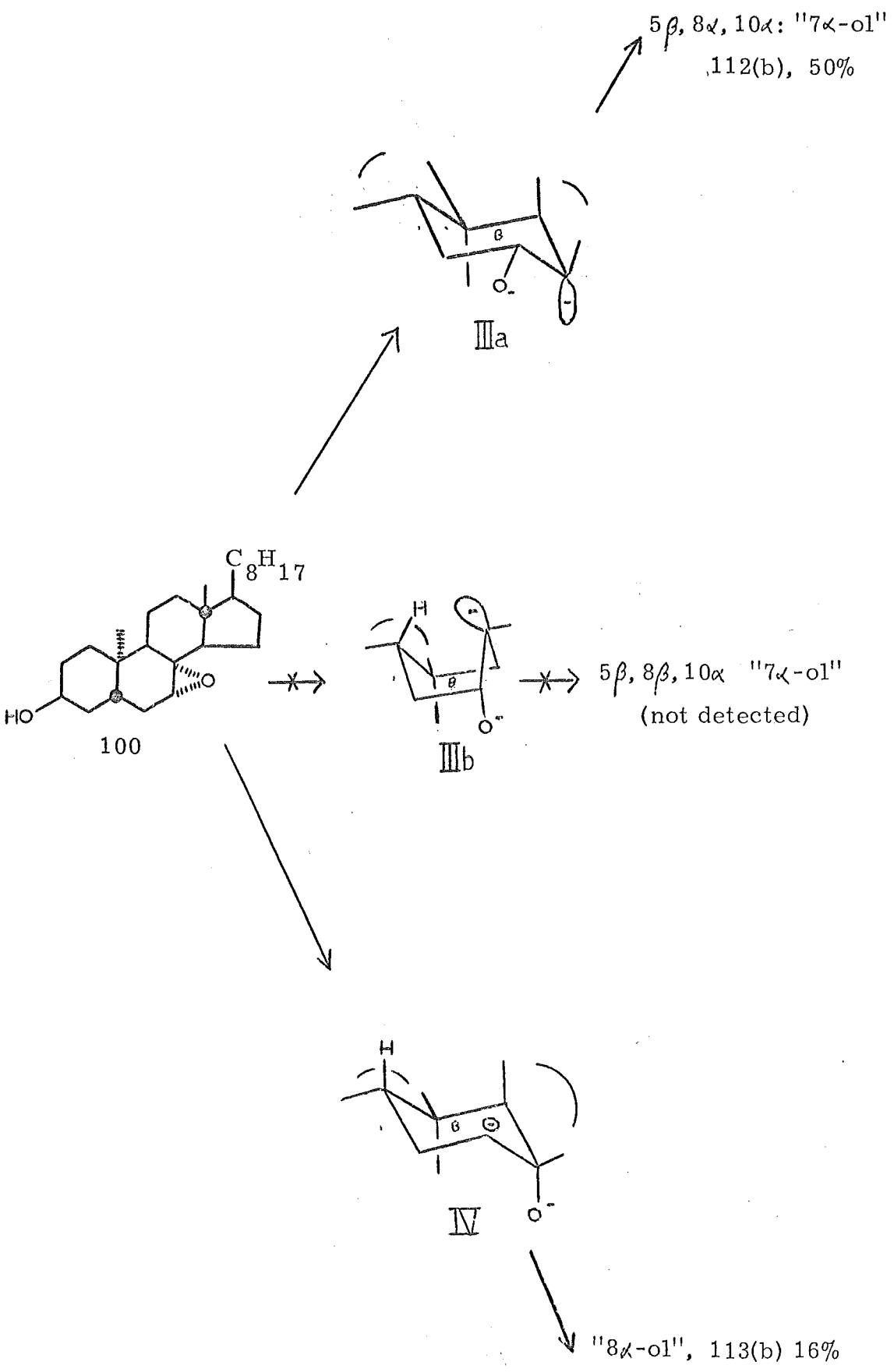

5β, 8α, 10α: "7α-ol"
112(b), 50%
IIIa
C8H17
HO
100
IIIb
5β, 8β, 10α "7α-ol"
(not detected)
IV
"8α-ol", 113(b) 16%

Fig. 52

conformation with the oxyanion in the flagpole position. The 7-oxygenated intermediate (II) is more stable in conformation (IIb), with ring B in a chair conformation and the anionic centres in an anti-relationship, than it would be in the alternative conformation (IIa) with ring B in a boat conformation and the anions more proximate. The observed diol product is the 3β, 7α-diol (e. g. 111a,109) having a C(8) β-configuration consistent with the intermediacy of IIb.

For the 10α-derivative (100) the possible reaction paths are shown in Fig. 52. In this skeletal isomer the 8α-hydroxy-derivative (113b) arises via an all chair intermediate (IV) and is isolated, as acetate, in 18% yield. The preferred C(8)-α-configuration in the 7α-oxygenated product (112b) can be rationalized in terms of the relative stabilities of the 'conformers' of the intermediate (IIIa, IIIb). As for the 'natural' analogues (IIa, IIb) the all-chair form is preferred and no product from the intermediate IIIb is observed.

Conclusions.

Reduction of the 10α-$\Delta^{5,7}$-diene (5h) with lithium-ammonia gave both A/B-trans (63%) and A/B-cis (15%) Δ^{7}-olefins (65c and 65d) but no Δ^{5}-olefin as previously reported in the D_2 series. Dissolving metal reductions, in general, give predominantly the thermodynamically more stable product. The relatively large yield of A/B-cis olefin (65d) indicates that the difference in thermodynamic stability between the A/B cis- and A/B-trans isomers is small.

Epoxidation of the 5β-Δ^{7}-olefin (65c) results in the exclusive formation of the 7α,8α-epoxide (100), a consequence of the severe steric hindrance of $C^{18}H_3$ to β-face attack at the C(7)-C(8) double bond. This factor also dominates the reactions of the 7α,8α-epoxide. Treatment of epoxide (100) under acidic conditions leads to rearrangement and no products of nucleophilic attack could be detected. The epoxide resists reduction by lithium aluminium hydride but is reduced by lithium-ethylamine where the steric requirement of the reductant is much smaller. The products of this reduction, and an analogous reduction in the natural series, can be rationalized in terms of relative stabilities of the dianions arising from a two electron addition to the epoxide.

The difference in reactivity between the Δ^5- and the Δ^7- olefinic bonds is also illustrated by the epoxidation of the $\Delta^{5,7}$-diene (5h) where no products of attack at the Δ^7-double bond could be detected. This is attributed to the steric hindrance to attack at this bond by $C^{18}H_3$ (β-face) and $C^{19}H_3$, C(9)H and C(14)H (α-face). Epoxidation of diene (5h) gave $5\beta,6\beta$-Δ^7-epoxide (72c, 60%); $3\beta,5\beta,6\alpha$-Δ^7-triol (70d; 25%) and a $3\beta,6\beta$-Δ^7-ether (71b, 12%). The triol (70d) was shown to arise from the breakdown of the $5\beta,6\beta$-epoxide (72c) under chromatographic conditions. The ether is believed to be formed from the $5\alpha,6\alpha$-Δ^7-epoxide (72d) which suffers rapid internal nucleophilic attack by the C(3)-hydroxyl group at C(6). The $C^{19}H_3$ group directs epoxidation at the Δ^5-olefin from the β-face (β:α; 7:1).

Various attempts to hydrogenate the Δ^7-triol (70d) were not successful and the major product was the $3\beta,5\beta$-Δ^7-diol (76a). In an attempt to increase the reactivity of the Δ^7-bond the triol was selectively oxidized at C(6). The Δ^7-bond in the enone (70f) did not, however, react with hydrogen in the presence of Adams catalyst or with sodium borohydride in pyridine. Reduction could be effected with lithium-ammonia but this was accompanied by considerable loss of the C(5)-

hydroxyl. The major product, 3β,5-dihydroxy-5β,10α-cholestan-6-one (84b, 32%) has the thermodynamically more stable C(8) configuration. This is in accord with the known stereochemical preference of such reactions and is also favoured by the directing influence of the C(5) oxy function. The failure to obtain saturated triol (84c or 84d) can be attributed to the inhibiting influence of the 5-oxy-anion on further reduction. The formation of this anion accounts for the retention of the 5-oxy function in the major product (84b). Due to the hindered position of the 5β-hydroxyl function reductive fission of the C(5)-O bond is competitive with anion formation and 5-deoxy products (85a, 84a, 84e) account for 49% of the total product mixture. The ratio of A/B-trans to A/B-cis deoxy products (5:2) reflects the small difference in thermodynamic stability between these isomers. This reduction has been shown to provide a feasible preparative route to saturated 10α-5-oxygenated steroids.

APPENDIX

In the determination of the configurations of some of the compounds described in this thesis, notably the reduction products of the enone (70f) and the epoxide (100), the chemical shifts of the angular methyl groups proved to be of great value. From a vast amount of data for natural steroids the relationship between these shifts and structure, especially substituent effects, is well-documented. Their diagnostic value was first noted by Schoolery and Rogers[158] who analyzed the spectra of forty seven mono- and multi-substituted 5α-steroids and assigned characteristic 'group frequency shifts' for the influence of functional groups on the chemical shifts of angular methyl groups. These substituent effects were observed to be additive in the examples studied. The concepts and observations of these authors have been extended by many other groups[159-70] and the "principle of additivity" is now well established. A notable contribution was made by Zurcher[87] who derived a comprehensive list of "additive shift values" to correlate the data of 265 steroids in the 5ξ,14ξ series. His method assumes that the difference

in chemical shift between two related compounds in which one has an additional function is due to the "shift value" of that function. Similar, but less comprehensive data, has been compiled by Jacquesy et al[171,172] and Tori and Komeno[173]. Capsi et al[174] have derived "shift values" for the influence of substituents on the chemical shift of the angular methyl in substituted estrones. Cohen and Rock[175] assumed that:

$$\tau = \tau_o + \Sigma b_i$$

where τ is an observed angular methyl shift; τ_o is the shift in 5α-androstane (114a) and b_i are substituent "additive shifts" a least squares analysis was then used to correlate the data of 292 5α-steroids. Additivity is assumed in this approach but unlike the 'Zurcher method' related pairs of compounds are not required. Lane[93] and Malinowski[176] used similar methods to derive shift values for some ringA and B substituents. "Additive shift values" have also been calculated for the influence of C(4), C(5) and C(6) substituents on the chemical shifts of C(3), C(4) and C(6) protons with[93] or without[173] geminal substituents. Halkes and Havinga[34] have reported "base" and "additive" shifts for the 5α-, 5β, 9β, 10α- (retro-), 5β, 8α, 10α-, and 5β, 9β- series but the additive shift data is limited. The 'base' values for these

series together with those for the 5β- and 5ξ,14β-series reveal a marked dependence of angular methyl shifts on skeletal structure. (Ref. Table 23 P.122 ; and subsequent discussion).

The influence of substituents on angular methyl shifts has been attributed to long range field effects (i.e. through space) with inductive effects having a minor influence[87,157,177]. Theory predicts that influences on chemical shifts arising from magnetic anisotropy and dipole effects are in fact additive[178,179]. Both of these field effects are dependent on the distance and orientation of the substituent vis-a-vis the methyl affected[177]. Therefore it may be expected that the same substituent at formally equivalent positions (vis-a-vis the methyl) will produce the same "additive shift"[176]. Indeed this is true in some cases (Table 13). However for oxy-

TABLE 13

Skeleton	Substituent	$\delta(C^{19}H_3)$ppm(a)
5α-	2β or 6βCl	+ 0.20
5α-	2α, 4α or 6α Br	+ 0.08
5α-	2β or 6β Br	+ 0.25
5α-	C(3) or C(7) keto	+ 0.23
5β-	2β or 4β Br	+ 0.05

(a) Data is that of Malinowski[176]; positive value implies a deshielding influence.

functions there is greater variation between formally equivalent positions; Table 7 (P. 87) shows the influence of hydroxyl groups 1,3-syn-diaxial to the affected methyl. These functions are not symmetrical and can rotate relative to the skeletal framework, (c.f. those in Table 13), and Zurcher[87] suggests that the observed differences may arise from different preferred conformations in the different positions. A notable instance is that of hydroxyl functions 1,2-anti-diaxial to the methyl, (Table 14)[173].

TABLE 14

Methyl	Hydroxyl	Additive Shift
$C^{18}H_3$	14α	+ 0.12
$C^{19}H_3$	5α	+ 0.18
$C^{18}H_3$	12α	+ 0.02
$C^{19}H_3$	1α	+ 0.04

In the present work analogies were drawn between unnatural and natural steroids in which the steric relationship of methyl and substituent were comparable. Where possible the expected change in an angular methyl shift with substituent was assessed by using 'shift values' from natural analogues. Because this always involved oxy-functions then these estimations

were necessarily of a qualitative nature. However the differences expected for the possible structures under scrutiny were sufficient to make reasonably confident assignments. In other cases (e.g. products from reduction of epoxide (100)) absolute values for angular methyl shifts were estimated. When a 'base' value was not available, one was estimated by consideration of the data in Table 23; additive values used were obtained from 'natural analogues'. As in the other method there was sufficient difference between calculated shifts for possible structures for confident assignments to be made.

'Base' and 'Additive' Shifts for Angular Methyls in the 5β, 8α, 10α-series.

The data of the twentynine compounds of this series which were prepared in this work were correlated empirically. Since they all had the C_8H_{17} side chain "base" values were estimated for 5β, 8α, 10α-cholestane (115a) and all other angular methyl shifts calculated from this base.

$C^{18}H_3$ Base Value. The relationship of the 17β-substituent to the $C^{18}H_3$ group is 1, 2-syn- (Fig. 11, P. 20 as in the natural series and therefore its 'additive shift value' should be the "natural value". Halkes and Havinga[34] observed

the $C^{18}H_3$ signal at δ0.70ppm in 5β, 8α, 10α-pregnane (115b) and therefore estimate a shift of δ0.84ppm for the $C^{18}H_3$ group in 5β, 8α, 10α-androstane* (115c). Similarly this chemical shift is ca δ0.79ppm in 5β, 8α, 10α-cholestane* (115a).

$C^{19}H_3$ Base Value There is no natural analogue for direct comparison in this instance. Halkes and Havinga[34] assume that the distance between 17β-alkyl and $C^{19}H_3$ is such that the difference in orientation between the natural and unnatural isomers is of little importance, i.e. they assume the shift values derived for 17β-alkyls in the natural series apply in the 5β, 8α, 10α-series. This approximation gives a value of δ0.92ppm for the $C^{19}H_3$ shift in 5β, 8α, 10α-cholestane (115a)[34].

Another estimation of the $C^{19}H_3$ shift in 5β, 8α, 10α-cholestane (115a) can be obtained from a comparison of pairs of 5α- and 5β, 8α, 10α-derivatives in which the steric relationships of substituents to the $C^{19}H_3$ group are formally equivalent (Table 15). For each pair substituent influences are regarded as identical and therefore the shift differences must be due entirely to the difference in skeletal structure. From the right

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*Relavent shift values are $\Delta\delta$(-0.14)ppm for 17β C_2H_5 and $\Delta\delta$(-0.05)ppm for 17β C_8H_{17}[87].

TABLE 15

Comparison of $C^{19}H_3$ Chemical Shifts for 5β8α10α-steroids and "natural analogues"

5β, 8α, 10α-cholestan-	(a) $\delta(C^{19}H_3)$	5α-cholestan-	(b) $(C^{19}H_3$	Δδ
3β, 6β-diol (84e)	0.92	3α, 6α-diol (116a)	0.77	0.15
3β, 6β-diol 6-acetate (84o)	0.97	3α, 6α-diol 6-acetate (116b)	0.82	0.15
3β, 6β-diol diacetate (84n)	0.98	3α, 6α-diol diacetate (116c)	0.84	0.14
3β-hydroxy- -6-one (84a)	0.85	3α-hydroxy- -6-one (116d)	0.72	0.13
3β, 6α-diol (84i)	1.12	3α, 6β-diol- (116e)	1.00	0.12
3, 6-dione (84g)	1.08	3, 6-dione (116f)	(c) 0.96	0.12
3β, 6α-diol diacetate (84h)	1.11	3α, 6βdiol diacetate (116g)	0.99	0.12
6-oxo- -3βyl acetate (84f)	0.88	6-oxo- 3α-yl acetate (116h)	0.75	0.13
3-oxo- -6βyl acetate (84p)	1.19	3-oxo- 6α-yl acetate (116i)	1.06	0.13

(a) Observed shift, this thesis

(b) Calculated values, from the data of Zurcher[87].

$$\Delta\delta = \delta(C^{19}H_3)_{8\alpha 10\alpha} - \delta(C^{19}H_3)_{5\alpha}$$

(c) Obs. shift, Zurcher[87].

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hand column of Table 15 it can be seen that the $C^{19}H_3$ signal in 5β, 8α, 10α-cholestane derivatives is ca 0.13ppm downfield of that in the 5α-analogues. This methyl is at δ 0.78ppm in

5α-cholestane (114b)[87] and therefore is estimated to be at ca δ0.91ppm in 5β, 8α, 10α-cholestane (115a).

TABLE 16

'Base' Values of Angular Methyl Shifts for 5β 8α10α-Steroids

	$\delta(C^{18}H_3)$ppm	$\delta(C^{19}H_3)$ppm
5β, 8α, 10α-pregnane (115a)	0.70[a]	0.93[a]
5β, 8α, 10α-androstane (115b)	0.84[b]	0.94[b]
5β, 8α, 10α-cholestane (115c)	0.79[c]	0.92[c] 0.91[d]

(a) Observed value; ref 34.

(b) Estimated value; ref 34

(c) Estimated value; P.105

(d) Estimated value, Table 15, Pp. 106-7

$C^{19}H_3$ Additive Shifts in the 5β, 8α, 10α-series: These were estimated by trial and error. Application of Zurcher's method[87] to the data for diol (84i) and triol (84k), and for the corresponding diacetates (84h, 84l), gave a value of $\Delta\delta$ (+0.06)ppm for the 5β-hydroxyl function. A comparison of the data for the 5β-hydroxy-6-ketones (84b, 84j, 84m) and the 5-deoxy-6-ketones (84a, 84f, 84g) implies a value of ca$\Delta\delta$ 0.02ppm for the 5β-hydroxyl (Table 17). This data is

TABLE 17

$C^{19}H_3$ shifts in substituted 5β, 8α, 10α-cholestan-6-ones

C(3)	5-hydroxy-compounds	$(C^{19}H_3)^a$	5-deoxy-compounds	$(C^{19}H_3)^a$	$\Delta\delta^a$
OH	84b	0.87	84a	0.85	+ 0.02
OAc	84j	0.88	84f	0.88	-
O	84m	1.11	84g	1.08	+ 0.03

(a) in ppm.

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best correlated by assuming a shift value of $\Delta\delta$(-0.04ppm) for the ketol function as a whole. In the natural series the use of individual additive shifts for C(5), C(6) ketols produces a marked deviation from the principle of additivity[173]. The value of $\Delta\delta$(+0.06)ppm reported by Zurcher[87] for the influence of the 5α-hydroxyl function on the chemical shift of the $C^{19}H_3$ in 5α-steroids is markedly different from that reported by other authors, viz $\Delta\delta$(0.17-0.20)ppm[180]. Inspection of Zurcher's data set[87] reveals only one 5α-hydroxy compound, 6-oxo-5α-androstane-3β, 5, 17β-triol 3-acetate, 17-benzoate (117), i.e. his value for $\Delta\delta$(5αOH) was derived from an example which is an exception to the general rule of additivity. This illustrates the need for caution in the derivation of such

values. For this reason the value of $\Delta\delta$ (+ 0.06)ppm for the influence of the 5β-hydroxyl on the $C^{19}H_3$ shift in the 5β8α10α-series (derived above) is best regarded as the 'shift value' for a 5β-hydroxyl function in the presence of a 3β-hydroxyl. Deviations from additivity have been noted for 3α, 5α-diols in the natural series.[173] The data set (Table 19) was insufficient to determine other "shift values" without arbitrarily assigning one of these. By analogy with the natural series the value for 3β-OH was set at 0.00ppm*; this and the other additive shifts are shown in Table 18a. The values in Table 18b follow by direct comparison of the relavent substituted steroid with 5β, 8α, 10α-cholestane (114b) - these represent substituents for which only one example is available. Table 18c contains examples where there is a marked deviation from additivity if individual additive shifts (Table 18a) are applied. These "multiple substituent effects" were assessed by trial and error. The value for C(5) - C(6) ketols has been discussed above (Table 17). Application of the data in Table 16 ('base')

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*Zurcher reports $\Delta\delta$ 0.00ppm for 3α-OH in 5α-natural steroids. In each case, 3α-OH in 5α-steroids and 3β-OH in the 5β, 8α, 10α series, the hydroxyl is 1,4-anti- with respect to $C^{19}H_3$.

and Table 18 ('additive') to the twentynine 5β, 8α, 10α-steroids involved gave the results shown in Table 19. A marked deviation is noted for the 3β, 5, 6α-oxygenated-Δ^7-olefins (70d, e, g) if the "multiple shift values" (Table 18(c) are used. The $\Delta\delta$ values for 6α-oxy- functions were derived from a saturated analogue and here they are applied in a Δ^7-olefinic skeleton. The 6α-oxy-function is 1, 3-syn-diaxial to the $C^{19}H_3$ group; in the natural series the 6β-oxy-functions are 1, 3-syn-diaxial to $C^{19}H_3$ and the different ability of the 5α- and 5β- skeletons to relieve this interaction is cited to account for the different shift values for the 6β- OR (R = Ac or H) function in 5α- and 5β- steroids[182]. For a similar reason the shift value derived in the 5β, 8α, 10α- saturated skeleton will give deviation from additivity when used in a Δ^7- skeleton. Another factor is that introduction of the Δ^7-olefinic bond alters the shape of the molecule and changes the orientation (and hence influence) of other substituents. The additivity of individual shift values (Table 18a) for these Δ^7-6 -oxy compounds (Ref. Table 20) is coincidental.

$C^{18}H_3$ Additive Shifts in the 5β, 8α, 10α-Series. These were estimated in the same manner as those for the $C^{19}H_3$ group. The value for the C(5) hydroxyl followed by Zurcher's method and other values were derived after a value of

$\Delta\delta$(-0.02)ppm had been assumed for the C(3)-ketone function[34]. The values in Table (18b) are self-explanatory. Application of the 'base' (Table 16) and 'additive' (Table 18) shift values gave the results shown in Table 20. The only discrepancies between 'observed' and 'calculated' shifts (e.g. C(5)-C(6) ketols) were minor. The apparent additivity of the $\Delta(\delta)$ values for the C(6)-ketone, C(5)-hydroxyl and Δ^7-olefin functions is probably coincidental.

A notable feature here is the greater sensitivity of the $C^{18}H_3$ chemical shift to ring A and ring B substituents than in the natural steroids. This is a consequence of the 'bent' nature of the 5β, 8α, 10α-skeleton which brings this methyl closer, relative to the natural skeleton, to these rings. In this isomeric skeleton the plane of rings C and D is perpendicular to that of rings A and B.

TABLE 18

Additive Substituent Shifts[a] for Angular Methyls in 5β, 8α, 10α- Steroids

	Substituent	No of Examples	$C^{19}H_3$	$C^{18}H_3$
A.	3β OH	13	0.00	+ 0.00
	3βOAc	11	+ 0.02	+ 0.01
	3-keto	5	+ 0.23	- 0.02
	5βOH	3	+ 0.06	+ 0.03
	6βOH	2	+ 0.01	+ 0.02
	6βOAc	3	+ 0.06	+ 0.00
	6αOH	3	+ 0.21	- 0.02
	6αOAc	4	+ 0.18	- 0.02
	6-keto	3	- 0.06	+ 0.07
	7α-OAc	1	+ 0.04	+ 0.03
	8α-OH	1	+ 0.31	+ 0.02
	Δ^7-	3	- 0.07	- 0.27
	7α, 8α-epoxy-	1	+ 0.16	- 0.07
B.	$\Delta^{5,7}$-3βOH	1	+ 0.19	- 0.24
	$\Delta^{5,7}$-3βOAc	1	+ 0.15	- 0.23
	Δ^7-5β, 6β-epoxy	1	+ 0.12	- 0.27
	$\Delta^{4,7}$-3, 6-dione	1	+ 0.44	- 0.26
C.	Δ^7-5βOH	2	+ 0.04	-
	5βOH, 6-keto	3	-0.04	-
	Δ^7-5βOH-6-keto	3	+ 0.03	-

(a) in ppm; +ve sign indicates a downfield shift (i.e. deshielding influence)

TABLE 19

$C^{19}H_3$ Chemical Shift for 5β, 8α, 10α-Series.

	$\delta(C^{19}H_3)$ ppm		
	Calc.	Obs.	Discrepancy
10α-cholesta-5, 7-dien-3β-ol (5h)	1.10	1.10	0.00
5β, 10α-cholest-7-en-3β-ol (65c)	0.84	0.83	+0.01
10α-cholesta-5, 7-dien-3β-yl acetate (5m)	1.06	1.06	-
5β, 10α-cholest-7-en-3-one (68)	1.07	1.07	-
5β, 10α-cholest-7-en-3β-yl acetate (65f)	0.86	0.84	+ 0.02
5β, 6β-epoxy-5β, 10α-cholestan-3β-ol (72c)	1.03	1.03	-
5β, 10α-cholest-7-ene3β, 5, 6α-triol (70d)	1.16 (1.11)	1.12	+ 0.04
5β, 10α-cholest-7-ene-3β, 5, 6α-triol 6-acetate (70g)	1.13 (1.08)	1.10	+ 0.03
5β, 10α-cholest-7-ene-3β, 5, 6α-triol, 3, 6-diacetate (70e)	1.15 (1.10)	1.10	+ 0.05
5β-hydroxy-5β, 10α-cholest-7-ene-3, 6-dione (77)	1.17 (1.07)	1.17	-
5β, 10α-cholest-7-ene-3β, 5-diol (76a)	0.95 (0.90)	0.95	-
3β, 5-dihydroxy-5β, 10α-cholest-7-en-6-one (70f)	0.94 (0.84)	0.95	-0.01
5β, 8α, 10α-cholestane-3β, 6β-diol (84e)	0.92	0.92	-
3β, 5-dihydroxy-5β, 8α, 10α-cholestan-6-one (84b)	0.87 (0.91)	0.87	-
5β, 8α, 10α-cholestane-3β, 6β-diol 6-acetate (84n)	0.97	0.97	-
5β, 8α, 10α-cholestane-3β, 6β-diol 3, 6-diacetate (84m)	0.99	0.98	+ 0.01
6-oxo-5β, 8α, 10α-cholestan-3β, 5-diol 3-acetate (84j)	0.89 (0.93)	0.88	-
6.0xo-5β, 10α-cholest-7-ene-3β, 5-diol 3 acetate (70j)	0.96 (0.86)	0.95	+ 0.01
3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a)	0.85	0.85	-

Table 19 continued.

	Calc.	Obs.	Discrepancy
5β, 8α, 10α-cholestane-3β, 5, 6α-triol (84c)	1.18	1.17	+ 0.01
5β, 8α, 10α-cholestane-3β, 6α-diol (84i)	1.12	1.12	-
5-hydroxy-5β, 8α, 10α-cholestane-3, 6-dione (84l)	1.10 (1.14)	1.12	-0.02
5β, 8α, 10α-cholestane-3, 6-dione (84g)	1.08	1.08	-
5β, 10α-cholest-7-ene-3β, 5β, 6β-triol (70h)	0.96	0.96	-
7α, 8α-epoxy-5β, 8α, 10α-cholestan-3β-ol (100)	1.07	1.07	-
5β, 8α, 10α-cholestane-3β, 7α-diol diacetate (112a)	0.97	0.97	-
5β, 8α, 10α-cholestane-3β, 8-diol 3-acetate (113a)	1.23	1.23	-
5β, 8α, 10α-cholestane-3β, 5β, 6α-triol 3, 6-diacetate (84k)	1.17	1.17	-
5β, 8α, 10α-cholestane-3β, 6α-diol diacetate (84h)	1.11	1.11	-
10α-cholest-4, 7-diene-3, 6-dione (78)	1.35	1.35	-
5-hydroxy-5β, 10α-cholest-7-en-3-one (76b)	1.18 (1.13)	1.18	-
6-oxo-5β, 10α-cholestan-3β-yl acetate (84f)	0.87	0.88	-0.01
3-oxo-5β, 10α-cholestan-6β-yl acetate (84o)	1.12	1.19	+ 0.01

( ) Values in brackets are derived by use of individual "shift values", Table 18(a) . The preceding values are derived from the data in Table 18c and, except in the case of the Δ^{7}-6-oxy-derivatives (70d, 70g, 70e), a better fit is obtained.

TABLE 20

$C^{18}H_3$ Chemical Shift in 5β, 8α, 10α Series.

	Obs	Calc	Disc.*
10α-cholesta-5, 7-dien-3β-ol (5h)	0.55	0.55	-
5β, 10α-cholest-7-en-3β-ol (65 c)	0.52	0.52	
10α-cholesta-5, 7-dien-3β-yl acetate (5m)	0.56	0.56	
5β, 10α-cholest-7-en-3-one (68)	0.50	0.50	
5β, 10α-cholest-7-en-3β-yl acetate (65f)	0.53	0.53	
5β, 6β-epoxy-5β, 10α-cholest-7- en-3β-ol (72c)	0.52	0.52	
5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d)	0.53	0.53	
5β, 10α-cholest-7-ene-3β, 5, 6α-triol 6-acetate (70g)	0.54	0.54	
5β, 10α-cholest-7-ene-3β, 5, 6α-triol 3, 6-diacetate (70e)	0.57	0.55	+ 0.02
5-hydroxy-5β, 10α-cholest-7-ene-3, 6-dione (77)	0.60	0.60	
5β, 10α-cholest-7-ene-3β, 5-diol (76a)	0.55	0.55	
3β, 5-dihydroxy-5β, 10α-cholest-7-en-6-one (70f)	0.63	0.62	+ 0.01
5β, 8α, 10α-cholestane-3β, 6β-diol (84e)	0.81	0.81	
3β, 5-dihydroxy-5β, 8α, 10α-cholestan-6-one (84b)	0.86	0.88	+ 0.02
5β, 8α, 10α-cholestane-3β, 6β-diol 6-acetate (84n)	0.78	0.79	-0.01
5β, 8α, 10α-cholestane-3β, 6β-diol 3, 6-diacetate (84m)	0.80	0.80	
6-oxo-5β, 8α, 10α-cholestane-3β, 5-diol 3 acetate (84j)	0.88	0.90	-0.02
6-oxo-5β, 10α-cholest-7-ene-3β, 5-diol 3 acetate (70j)	0.63	0.63	
3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a)	0.85	0.86	-0.01

Table 20 continued.	Obs	Calc	Disc.
5β, 8α, 10α-cholestane-3β, 5, 6α-triol (84c)	0.80	0.80	
5β, 8α, 10α-cholestane-3β, 6α-diol (84i)	0.77	0.77	
5-hydroxy-5β, 8α 10α-cholestane-3, 6-dione (84l)	0.85	0.86	-0.01
5β, 8α, 10α-cholestane-3, 6-dione (84g)	0.83	0.83	
5β, 10α-cholest-7-ene-3β, 5, 6β-triol (70h)	0.56	0.57	-0.01
7α, 8α-epoxy-5β, 8α, 10α-cholestan-3β-ol (100)	0.72	0.72	
5β, 8α, 10α-cholestane-3β, 7α-diol diacetate (112a)	0.83	0.83	
5β, 8α, 10α-cholestane-3β, 8-diol 3-acetate (113a)	0.82	0.82	
5β, 8α, 10α-cholestane-3β, 5, 6α-triol 3, 6-diacetate (84k)	0.82	0.82	
5β, 8α, 10α-cholestane-3β, 6α-diol diacetate (84h)	0.78	0.79	-0.01
10α-cholesta-4, 7-diene-3, 6-dione (78)	0.53	0.53	
5-hydroxy-5β, 10α-cholest-7-en-3-one (76b)	0.53	0.53	
6-oxo-5β, 10α-cholestan-3β-yl acetate (84f)	0.88	0.87	+ 0.01
3-oxo-5β, 10α-cholestan-3β-yl acetate (84p)	0.78	0.77	+ 0.01

* Discrepancy = δ(observed)-δ(calculated).

Base and Additive Shifts in the 5α, 10α-Steroids

The $C^{19}H_3$ chemical shift in 5α, 10α-cholestane (118) can be estimated from a consideration of the data for the dione (85h). The C(3) ketone function is γ to the axial $C^{19}H_3$ and therefore deshields these protons by ca 0.23ppm*; likewise the C(6)-ketone function deshields the $C^{19}H_3$ by ca 0.20ppm since its relationship to this methyl is analogous to that between the C(4)-ketone and $C^{19}H_3$ groups in A/B-cis-natural steroids.** The chemical shift of the $C^{19}H_3$ in dione (85h) is δ1.35ppm and therefore for 5α, 10α-cholestane:-

$$\delta(C^{19}H_3) = 1.35 - [0.23 + 0.20] = 0.92\text{ppm}.$$

This is the same as observed in 5β, 8α, 10α-cholestane (115c; Table 16). In the 5α, 10α-isomer this methyl is equatorial to, and thus deshielded by, ring B; but it is shielded by the C(9)-C(11) bond. Conversely the $C^{19}H_3$ in the 5β, 8α, 10α-isomer is axial to both A and B, and therefore shielded, but is in the deshielding region of C(9)-C(11), (Fig. 55 , P. 124).

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*$\Delta\delta$ = +0.23ppm for the influence of C(3) and C(7) ketone functions on the chemical shift of $C^{19}H_3$ in 5β-steroids[87].

**$\Delta\delta$ = +0.20ppm for the influence of the C(4) ketone function on the $C^{19}H_3$ shift in 5α-steroids[87].

There was insufficient data to permit an estimation of the $C^{18}H_3$ chemical shift in 5α,10α-cholestane. The local environment of this methyl is the same as in 5α-cholestane, and the only difference in total environment is in the orientation of ring A for which there is no direct analogy. In natural 5ε-steroids ring A is coplanar with the 'steroidal plane' (5α-) or perpendicular to it and on the α-face. Because of the distance between ring A and $C^{18}H_3$ this variation has no effect on the chemical shift of this methyl. In 5α,10α-isomers ring A is perpendicular to, and on the β-face of the 'steroidal plane'. From the discussion on Δ^7-olefins (Pp.24-6) the $C^{18}H_3$ is deshielded by ca 0.03ppm in the 5α,10α-Δ^7-skeleton relative to that in the 5α-, 5β-, and 5β,10α-Δ^7-skeletons. However in these cases there is a 3β-hydroxyl function and a Δ^7-olefinic bond which alters the steric relationship of $C^{18}H_3$ to ring A relative to that in a fully saturated skeleton. If the influences of these differences are ignored then the $C^{18}H_3$ shift in 5α,10α-cholestane is estimated to be ca 0.66ppm*.

Additive shifts for the influence of substituents on the

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* ($C^{18}H_3$) in 5ε-cholestane is 0.63ppm[87]; effect of variation at C(5)-C(10) estimated as ca ±0.03ppm.

$C^{19}H_3$ chemical shift were estimated by trial and error with the values for the C(3)- and C(6)- ketone functions as assumed in the derivation of the base value. This data is summarized in Table 21 and application of this to the 5α,10α-steroids gives the results tabulated in Table 22.

TABLE 21. ADDITIVE SHIFTS FOR $C^{19}H_3$ IN 5α, 10α-STEROIDS

SUBSTITUENT	ADDITIVE SHIFT	No. of examples
3β-hydroxyl	0	3
3β-acetoxyl	+0.03	2
3-oxo	+0.23	2
6-oxo	+0.20	1
6α-hydroxyl	+0.08	1
6α-acetoxyl	+0.11	3
Δ^{7}	+0.01	2
$\Delta^{5,7}$-3βOH	+0.18	1
$\Delta^{5,7}$-3βOAc	+0.14	1
Δ^{7}-3β,6β-oxido-5α-hydroxy	+0.13	1
$\Delta^{4,7}$=3,6-dione	+0.43	1

*+ve value implies deshielding influence.

TABLE 22. $C^{19}H_3$ SHIFTS IN 5α, 10α-STEROIDS

	($C^{19}H_3$)		
	CALC	OBS	
10α-cholesta-5, 7-dien-3β-ol (5h).	1.10	1.10	-
5α, 10α- cholest-7-en-3β-ol (65d)	0.93	0.93	-
10α-cholesta-5, 7-dien-3β-yl acetate (5m)	1.06	1.06	-
3β, 6β-oxido-5α, 10α-cholest-7-en-5-ol (71b)	1.05	1.05	-
5α, 10α-cholestane-3β, 6α-diol (85h)	1.00	1.00	-
5α, 10α-cholestane-3β, 6α-diol 7α acetate (85e)	1.03	1.03	-
5α, 10α-cholestane-3, 6-dione (85h)	1.35	1.35	-
3-oxo-5α, 10α-cholestane-6α-yl acetate (85g)	1.26	1.28	-0.02
10α-cholesta-4, 7-diene-3, 6-dione (78)	1.35	1.35	-
5α, 10α-cholestane-3β, 6α-diol diacetate (85f)	1.06	1.05	+0.01

TABLE 23. ANGULAR METHYL SHIFTS IN ISOMERIC ANDROSTANES

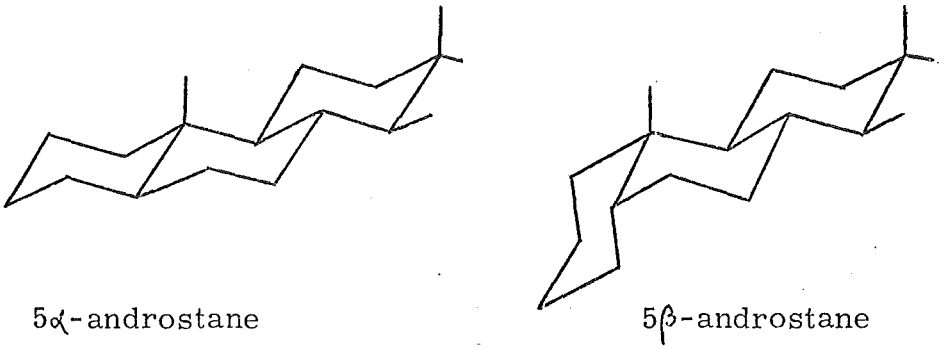
	ISOMER[d]	($C^{19}H_3$)	($C^{18}H_3$)
I	5α-	0.79[a,b]	0.69[a,b]
II	5α, 14β-	0.77[a]	0.99[c]
III	5β, 14β-	0.90[a]	0.99[a]
IV	5β-	0.92[a]	0.69[a]
V	5β, 10α, 9β-	0.95[b]	0.72[b]
VI	5β, 8α, 10α-	(0.94)[b,c,e]	(0.84)[b,e]
VII	5α, 9β-	(0.91)[b,e]	(0.90)[b,e]
VIII	5α, 10α-	(0.92)[c,e]	(0.71)[c,f]

(a) Ref. 87. (b) Ref. 34. (c) This thesis. (d) Assume a 5ξ, 8β, 9α, 10β, 13β, 14α, 17β-stereochemistry unless otherwise indicated. (e) Estimated shift, not an observed value. (f) Very approximate.

From the data for the 5ξ, 14ξ-androstanes it has been noted that "as a given angular methyl is able to see less of the remainder of the molecule it will resonate at a lower field"[182]. For example in the 5α-isomer (I) the skeleton is approximately planar with the $C^{19}H_3$ above and overlooking

it, the shift is 0.79; but in the 5β-isomer (IV) ring A is perpendicular to the steroid plane and the methyl no longer is above and overlooking ring A and the chemical shift is 0.92ppm. (Fig. 53). In other words the methyl is axial to ring A in the 5α-isomer (I) and equatorial to A in the 5β-isomer (IV) with its relationship vis-a-vis the rest of the molecule identical in each isomer. Equatorial protons are deshielded relative to axial protons[146]. In the series I, II, III and IV (Table 23), the $C^{19}H_3$ shift is insensitive to the configuration at C(14). Likewise the $C^{18}H_3$ shift is markedly affected by the configuration at C(14) but is not influenced by that at the more distant C(5) centre.

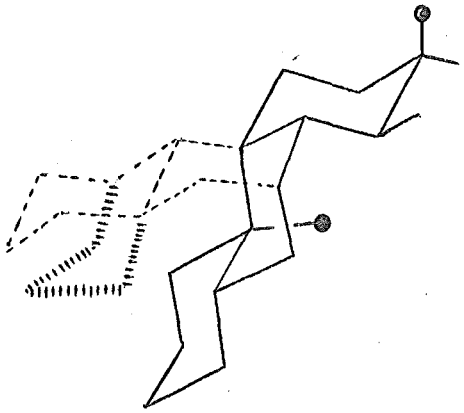
In the retro-isomer (V) (Fig. 54) the bent nature of the skeleton means that the $C^{18}H_3$ can 'see' less of rings A and B than in the natural isomer ; i.e. relative to the natural isomer rings A and B have moved away from $C^{18}H_3$. Since the structural variation is not in the immediate environment of the $C^{18}H_3$ then the influence is small - it is deshielded by 0.03ppm relative to the $C^{18}H_3$ in 5α-androstane (I). The $C^{19}H_3$ is axial to rings A and B just as in the natural isomer (I) but, relative to that isomer rings C and D are markedly closer-this leads



5α-androstane

5β-androstane

Fig. 53.



Retro-androstane

5α-androstane

5β-androstane

Fig. 54.

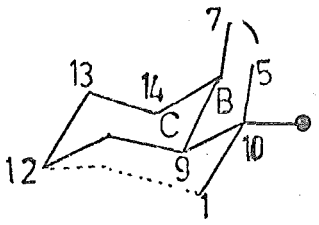


Fig. 55

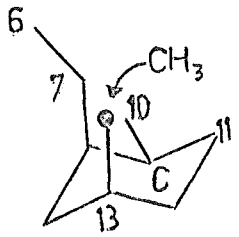


Fig. 56

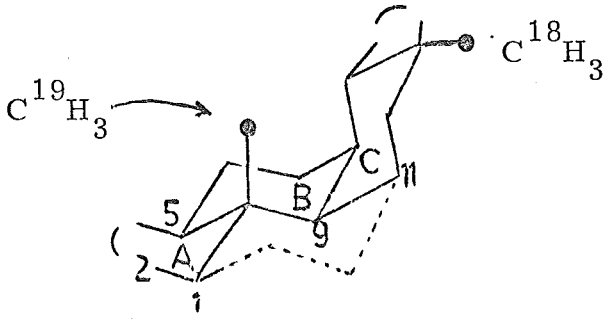


Fig. 57

to a deshielding effect of 0.16ppm relative to isomer (I). This is contrary to the previously quoted generalization (P. 122) and inspection of the data set in Table 23 together with relevant Dreiding models reveals that this may best be rephrased as "deviations from planarity in the steroid skeleton cause deshielding of angular methyl groups".

8-iso-10-iso:- Here the $C^{19}H_3$ is axial to rings A and B, just as in the natural series, but the inversion at C(8) and C(10) brings this methyl into the deshielding region of the C(9)-C(11) bond, Fig. 55. Inspection of Dreiding models shows that C(12)-C(11)-C(9)-C(10)-C(1) are oriented in the manner of a chair ring (-----, Fig. 55) in which $C^{19}H_3$ is equatorial; in natural steroids inversion from 5α- to 5β- causes this methyl to become equatorial to ring A and results in a deshielding of 0.13ppm. The $C^{18}H_3$ group is syn-diaxial to the $C^{7}H_2$ moiety (Fig. 56), and the deshielding of this methyl (relative to that in 5ξ-naturals) can be attributed to the anisotropy of the C(6)-C(7) bond and the van der Waals compression effect between $C^{7}H_2$ and $C^{18}H_3$.

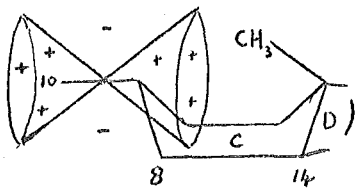
9β10α:- In this skeleton the $C^{19}H_3$ group is syn-diaxial to both C(8)-C(14) (in ring B) and C(11)-C(12) (in the

"part chair" formed by C(1),(9),(10),(11)), Fig.57, and the deshielding of this methyl (relative to 5ξ-naturals) is attributable to the van der Waals effect. The $C^{18}H_3$ is ca 0.03ppm downfield of that in 5ξ-steroids. In 5ξ-steroids inversion from C(5)α- to C(5)β has no effect on the $C^{18}H_3$ resonance - ring A moves away from $C^{18}H_3$ but the distance between A and $C^{18}H_3$ makes the influence of this variation negligible. For a 9β,10α steroid, both rings A and B 'move away' from $C^{18}H_3$, relative to the situation in 5ξ-steroids (Fig. 54). The molecular change in this case is closer to the methyl and a small deshielding influence (ca 0.03ppm) is noted.

9β :- In the conformation with ring C as a boat the relationship of C(9)-C(11) and $C^{19}H_3$ is approximately the same as that observed in the 8α,10α-skeleton. In each of these skeletons this methyl is ca 0.12-0.15ppm downfield of the "natural position". The deshielding of the $C^{18}H_3$ group, relative to that in the natural series, could, at least in part, be attributable to the anisotropy of the C(10)-C(9) bond (Fig. 58).

In the conformation where ring B is a boat then rings A and B are perpendicular to, and below, the steroidal plane. This is similar to the situation for the 'retro'-skeleton, Fig. 54, where this distortion (relative to the

natural structure) causes a 0.03ppm deshielding of the $C^{18}H_3$ group. Any differences between the 9β- and 9β,10α skeleton are well removed from the $C^{18}H_3$ methyl so in this conformation it is difficult to account for the downfield position of the $C^{18}H_3$ ($\delta(9\beta)-\delta(\text{natural}) = 0.21$ppm). Similarly it is difficult to account for the deshielding of the $C^{19}H_3$ group; i.e. the angular methyl resonances favour the "C-boat" conformation of 9β-steroids.



\+ = deshielding zone of C^9-C^{10} bond in 9β-steroid with boat ring C

Fig. 58

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined for ethanol solutions at 25°C in a 10mm quartz cell on an ETL-NPL automatic polarimeter. Optical rotatory dispersion and circular dichroism curves were measured on a JASCO Optical Rotatory Dispersion Recorder Model ORD/UV-5. Ultra-violet absorptions were determined for cyclohexane or methanol solutions in 1mm or 10mm quartz cells on a Shimadzu MPS-5OL spectrometer. Infrared spectra were recorded on a Shimadzu 27-9 spectrometer using KBr discs unless otherwise stated. NMR spectra were recorded for ca 10% w/v $CDCl_3$ solutions, with TMS as an internal reference, on a Varian A-60 or Varian T-60 spectrometer. Micro-analyses were determined at the University of Otago. Mass spectra were recorded on an AEI Model MS9 spectrometer. Commercial spectroscopically pure solvents were used for all spectra.

The alumina used for column chromatography was P Spence Grade H deactivated by the addition of 5% v/v or 10% v/v of 10% aqueous acetic acid. Solvents used for chromatography were purified technical grade. Benzene

and petroleum ether were distilled off phosphorous pentoxide and ether was distilled off sodium hydride. Petroleum ether refers to the fraction of b.p 50-70°.

Merck silica gel with binder and Fluka alumina type H were used for TLC. Chromatograms were developed using benzene, chloroform, chloroform-acetone, and chloroform-methanol elutants. The visualizing agents used were iodine and phosphomolybdic acid in ethanol.

Preparation of 9β-cholesta-5,7-dien-3β-ol (5i) and 10α-cholesta-5,7-dien-3β-ol (5h)

A solution of Vitamin D_3 (7b; 50gm) in decalin (40ml) was refluxed under nitrogen, in the dark, for two hours. The mixture was then cooled, diluted with benzene (200ml) and adsorbed onto 5% deactivated alumina (1Kg). The column was protected from light and the eluting solvent was de-aerated and had nitrogen continuously bubbled through it.

Benzene eluted a gum containing decalin followed by unidentified mixtures (8gm), also as gums.

Further elution with benzene, and then with ether, gave 9β-cholesta-5,7-dien-3β-ol (5i, 24.6gm) as a gum, (pure by TLC); $[\alpha]_D$ + 184° (c 1.025); ν_{max} (film) 3331cm^{-1}, NMR:

δ 5.63 (J = 6Hz; C^7-H); 5.24, 5.29, 5.34, 5.38, 5.43, 5.49 (C^6-H); 3.47 ($W_{h/2} \approx$ 20Hz; C^3-H); 1.24 (C^{19}-H_3); 0.64 ($C^{18}H_3$), 0.92, 0.83ppm (side chain methyls).

The decalin containing gum was diluted with petroleum ether and recolumned on 5% deactivated alumina (200gm). Elution with petroleum ether removed the decalin. Elution with benzene gave 10α-cholesta-5, 7-dien-3β-ol (5h; 17.4gm) as needles (pentane); m.p. 78-80°; $[\alpha]_D$ + 154° (c 1.03); ν_m 3328, 1648, 1658cm^{-1}; λ_m 266nm (shoulder, ϵ 9810), 276nm (ϵ13870), 286nm (ϵ14930), 299nm (ϵ8750); CD (cyclohexane) λ_m264nm (shoulder, $\Delta\epsilon$ + 12.8), 274nm ($\Delta\epsilon$ + 18.1), 284 ($\Delta\epsilon$ + 16.9), 296nm ($\Delta\epsilon$ + 9.7); ORD (cyclohexane), $[\phi]_{235}$ 19810°, $[\phi]_{257}$ -32060° (trough), $[\phi]_{277}$ 0°, $[\phi]_{292}$ + 34390° (peak), $[\phi]_{295}$ + 32060° (trough), $[\phi]_{302}$ + 42550° (peak), $[\phi]_{325}$ + 15740°, $[\phi]_{350}$ + 8740°, $[\phi]_{375}$ + 6410°, $[\phi]_{400}$ + 5250°, a = + 746; NMR, δ 5.57 (J = 1.5Hz), 5.47 (J = 1.5Hz) (d, J = 6Hz, C^6-H); 5.23, 5.33 (d, J = 6Hz; C^6-H); 4.02 (t, J = 3Hz; C^3-H), 1.98 (removed by D_2O shake, OH); 1.10 (C^{19}-H_3); 0.55 (C^{18}-H_3); 0.03, 0.82 (side chain methyls).

The mixed fractions (8gm) from the initial chromatography, were adsorbed onto 5% deactivated alumina (500 gm) Elution with benzene-petroleum ether (1:1) gave 10α-cholesta-5, 7-dien-3β-ol (5h; 1.93gm) followed by a mixture (3.72gm) of

unidentified compounds. Elution with benzene gave 9β-cholesta-5, 7-dien-3β-ol (5i, 2. 3gm).

Lithium-ammonia reduction of 10α-cholesta-5, 7-dien-3β-ol (5h)

Lithium metal (6. 2gm) was added carefully to a stirred solution of 10α-cholesta-5, 7-dien-3β-ol (5h; 9. 37 gm) in dry ether (250ml) and liquid ammonia (250ml; distilled off sodium immediately prior to use). When all the lithium had dissolved, ethanol was slowly added until the blue colour of the solution was discharged. The mixture was diluted with water and left open to the atmosphere to allow the ammonia to evaporate. The steroidal material was extracted with ether and the solvent was removed in vacuo on a water bath. The crude product (9. 3gm) was adsorbed onto 5% deactivated alumina (400gm).

Elution with petroleum ether gave an unidentified gum (136mg). Elution with benzene-petroleum ether (1:4) gave 5β, 10α-cholest-7-en-3β-ol (65c; 6. 35gm) as needles (pentane-ether); m. p 110-1°; $[\alpha]_D$+ 145. 2 (c 1. 04); ν_{max} 3325, 1002 cm^{-1}; λ_m (cyclohexane) 198 nm (ϵ 5712); NMR, δ 5. 18 ($W_{h/2}$ 7Hz; C^7-H), 4. 05 ($W_{h/2}$ 6Hz , C^3-H) 0. 83 ($C^{19}H_3$), 0. 55 ($C^{18}H_3$), 0. 91, 0. 82 (side chain methyls). (Found:

C, 83.67; H, 11.91%. $C_{27}H_{46}O$ requires: C, 83.85; H, 12.01%).

Elution with benzene-petroleum ether (7:3) gave 5α, 10α-cholest-7-en-3β-ol (65d; 700mg) as a gum; ν_{max} 3360cm^{-1}; NMR, δ 5.15 ($W_{h/2}$ 7Hz, C^7-H), 3.78 ($W_{h/2}$ ca 15Hz; C^3-H) 0.93 ($C^{19}H_3$), 0.55 ($C^{18}H_3$), 0.82, 0.92ppm (side chain methyls).

5β,10α-Cholest-7-en-3-one (68)

Chromic acid (8N) was added dropwise to a stirred solution of 5β,10α-cholest-7-en-3β-ol (65c, 96mg) in dry acetone (4ml) until there was a residual red coloration. Excess reagent was quenched by addition of aqueous sodium metabisulfite and the steroidal material (86mg) isolated *via* dichloromethane. Filtration of the crude product through 5% deactivated alumina gave 5β,10α-cholest-7-en-3-one (68; 70mg) as flakes (acetone); m.p. 117-8°; ν_m 1711cm^{-1}; λ_m (cyclohexane) 201nm (ε4580), 280nm (ε11); CD, λ_m 290nm ($\Delta\epsilon_m$ - 0.096); NMR, δ 5.18 ($W_{h/2}$ 8Hz; C^7H), 1.07 ($C^{19}H_3$), 0.50 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 84.21; H, 11.43%. $C_{27}H_{44}O$ requires: C, 84.08; H, 11.33%).

Attempted isomerizations of 5β,10α-cholest-7-en-3-one (68).

5β,10α-Cholest-7-en-3-one (68; 19mg) in petroleum

ether was adsorbed onto active alumina (5gm) and left for twelve hours. Elution with ether-ethanol (9:1) gave unchanged 5β,10α-cholest-7-en-3-one (68; 18mg) identified by IR, NMR and m.p (117-8^0).

A solution of 5β,10α-cholest-7-en-3-one (68; 20mg) in 5% methanolic sodium hydroxide was heated for two hours under reflux in a nitrogen atmosphere. The solution was diluted with dilute sulfuric acid (2%) and extracted with ether to yield unchanged starting material (68, 18mg) identified by spectral data and melting point (116-8^0). In particular the Ultra-violet spectrum showed no evidence of a conjugated enone moiety.

5β,10α-cholest-7-en-3β-yl acetate (65f)

Acetic anhydride (0.8ml) was added to a solution of 5β,10α-cholest-7-en-3β-ol (65c; 540mg) in pyridine (5ml). After standing at room temperature overnight the mixture was heated on a steam bath for two hours. The crude product (485mg), isolated *via* ether gave 5β,10α-cholest-7-en-3β-yl acetate (65f, 406mg) as needles (acetone); m.p. 162-3^0 ν_m 1720, 1245, 1228cm^{-1}; λ_m (cyclohexane) 201.5nm (ε 7120); $[\alpha]_D$ + 213^0 (C. 1.05); NMR, δ 5.13 ($W_{h/2}$ 7Hz, C^7-H), 4.98 ($W_{h/2}$ 9Hz, C^3-H), 2.02 (CH_3CO_2-), 0.84 ($C^{19}H_3$), 0.53 ($C^{18}H_3$), 0.84, 0.92 (side chain methyls)ppm. (Found: C, 81.41,

H, 11.47%. $C_{29}H_{48}O_2$ required: C, 81.25; H, 11.47%).

Reaction of 10α-cholesta-5,7-dien-3β-ol with monoperoxyphthalic acid.

A solution of mono-peroxyphthalic acid (ca 0.15M) in ether (25ml) was added to a solution of 10α-cholesta-5,7-dien-3β-ol (5h , 980mg, ca 0.0025 moles) in dry ether (50ml) at $0^{\circ}C$. The mixture was stirred for two hours at $0^{\circ}C$ and then washed with aqueous bicarbonate. The organic phase was dried over sodium sulfate and the solvent removed in vacuo. The crude product (751mg) was adsorbed onto 5% deactivated alumina (70gm).

Elution with benzene-petroleum ether mixtures (2:3 to 4:1) gave mixtures (34mg) which were not further investigated. Elution with benzene gave a gum (35mg); NMR: δ 4.33 ($W_{h/2}$ 10Hz; CHOH), 4.08 (d, J 2Hz), 3.69 (d, J 2Hz), 3.15 (removed by D_2O shake), 1.07 ($C^{19}H_3$), 0.77 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls) ppm.

Elution with benzene-ether (9:1) gave a gum (96mg); NMR: δ 5.375 (IH, d, J 5Hz), 4.38 ($W_{h/2}$ 10Hz; CH-OH), 3.94(1H, d, J 5Hz), 1.12 ($C^{19}H_3$), 0.62 ($C^{18}H_3$), 0.825, 0.925 (side chain methyls)ppm.

Elution with ether-methanol (99:1) gave mixtures

(438mg) which were not investigated further. TLC indicated these mixtures to contain a number of compounds of similar polarity.

Reaction of 10α-cholesta-5,7-dien-3β-ol (5h) with meta-chloro-perbenzoic acid

Metachloro-perbenzoic acid (670mg; 3.88 m.mole) in ether (50ml) was added to a solution of 10α-cholesta-5,7-dien-3β-ol (5h, 960mg, 2.50m.mole) in ether (50ml) at 0°C. After stirring for five minutes the mixture was washed with aqueous sodium bicarbonate (2x100ml), aqueous sodium carbonate (5×100ml), water (2x100ml), brine (1x100ml) and dried over sodium sulphate. The solvent was removed in vacuo and the crude product (795mg) adsorbed onto 5% deactivated alumina (50gm). Elution with benzene-petroleum ether (3:2 and 1:1) gave a gum (154mg) shown by TLC to be a mixture of compounds. From the NMR spectrum of this mixture it appeared to contain 5β,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c) and another compound with the following NMR: δ 5.58 (1H, d, J = 5Hz, C = C=H)*, 3.93 ($W_{h/2}$ 8Hz, CHOH)

*In a double irradiation experiment these doublets collapse with a difference frequency of +152 and -152Hz.

3.05 (1H, d, J = 4Hz; C(O)C-H) 1.23 ($C^{19}H_3$), 0.69 ($C^{18}H_3$) 0.83, 0.93 (side chain methyls). Attempts at further purification gave a small amount of the mixture plus decomposition products and this separation was not further investigated.

Elution with benzene-petroleum ether (1:1) gave mixtures (349mg) of 5β,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c) and 3β,6β-oxido-5α,10α-cholest-7-en-5-ol (71b). Further recolumning yielded pure samples of these compounds, the full data for which is given on Pp.140-1 . Elution with benzene-petroleum ether (4:1) gave unresolved mixtures (302mg) which were not further investigated.

10α-Cholesta-5,7-dien-3β-yl acetate (5m)

Acetic anhydride (1.5ml) was added to a solution of 10α-cholesta-5,7-dien-3β-ol (5h) in pyridine. After fifteen hours at room temperature the mixture was heated for several hours on a steam bath. The crude product (1.65gm), isolated via ether, gave 10α-cholesta-5,7-dien-3β-yl acetate (5m; 1.35gm) as needles (methanol); m.p 121-2°; $[\alpha]_D$ + 401° (C 1.02); Literature values[87]; m.p 121°, $[\alpha]_D^{19}$ + 438 ; ν_{max} 1730, 1250 (multiplet) cm^{-1}; λ_{max} (cyclohexane) 266nm (shoulder, ε 6875), 275nm (ε9640), 286nm (ε10110);

NMR, δ 5.48, 5.38, 5.33, 5.23 (AB quartet; $J_{C^6\text{-}(H),\ C^7(H)}$ = 6Hz; C^6H, C^7H), 4.95 ($W_{h/2}$ = 9Hz, C^3-H), 1.95 (CH_3CO_2), 1.06 ($C^{19}H_3$), 0.56 ($C^{18}H_3$), 0.825, 0.925 (side chain methyls) ppm. (Found: C, 81.53; H, 10.87%. $C_{29}H_{46}O_2$ requires: C, 81.63; H, 10.71%).

Reaction of metachloroperbenzoic acid and 10α-cholesta-5,7-dien-3β-yl acetate (5m).

Metachloro-perbenzoic acid (907mg; 3.5m. moles) in ether (50ml) was added to a solution of the acetoxy-diene (5m; 1033mg; 2.42m. mole) in ether (50ml) at 0°C and the mixture stirred for three minutes. It was then washed with aqueous sodium bicarbonate (2x100ml), aqueous sodium carbonate (5x100ml), water (2x100ml), brine (1x100ml) and dried over sodium sulphate. Removal of the solvent in vacuo afforded a crude product (935mg) which was adsorbed onto 5% deactivated alumina (50gm).

Elution with benzene-petroleum ether (9:1) gave an epoxide mixture (238mg) as needles (acetone); NMR δ 5.58 (d*, J = 4Hz, $C\overset{O}{\overset{/\backslash}{-}}C\text{-}C{=}C\text{-}H$), 4.9 ($W_{h/2}$ = 8Hz $C\underline{H}$-OAc), 3.05 (d* J = 4Hz, $C\overset{O}{\overset{/\backslash}{-}}\underset{H}{C}\text{-}C{=}C\text{-}$), 1.97 ($CH_3CO_2$), 1.25 ($C^{19}H_3$),

*In a double irradiation experiment one doublet collapses when the difference frequency is + 152Hz or -152Hz.

0.71 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm; and NMR δ 5.38 (d, J = 4Hz, $C^{\overset{O}{\|}}-C-C=C-H$),* 4.9 ($W_{h/2}$ 8Hz, $C\underline{H}OAc$), 2.7 (d, J = 4Hz, $C^{\overset{O}{\|}}-\underset{H}{C}-C=C$),* 1.97 ($CH_3CO_2$), 1.06 ($C^{19}H_3$), 0.56 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. Further attempts at separating this mixture by fractional recrystallization and re-columning were not successful. The NMR data for the components was deduced from data for a series of mixed fractions.

Elution with benzene-petroleum ether (3:2 through to 100:0) gave unresolved mixtures (433mg) of compounds. NMR data indicated that one of the components had the following spectra, δ 6.07 (d, J = 10Hz) 5.33 (d, J = 10Hz), 4.91 ($W_{h/2}$ = 6Hz), 1.92 (CH_3CO_2) 1.00 ($C^{19}H_3$), 0.88 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm.

Preparation of Perbenzoic Acid

Sodium (3.1gm) was dissolved in absolute methanol (60ml) and the solution cooled to -5^0. A freshly prepared solution of benzoyl peroxide (commercially pure, 30gm) in cold chloroform (60ml) was added carefully with shaking and cooling such that the temperature was kept below 0^o.

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*Double irradiation experiment collapses one doublet when the difference frequency is + 162c/s or -162c/s.

After stirring for five minutes the reaction mixture was extracted into iced water (300ml) which was then washed with chloroform (2x100ml) to remove methyl benzoate. Addition of cold 1N sulphuric acid (135ml) liberated the perbenzoic acid which was then extracted into chloroform (3x60ml) and back-washed with water (2 x30cc). The solution was dried over sodium sulphate and stored at O^{o} in the dark. Immediately before use the peracid strength was determined by iodometric assay. Yield 7.94gm (46%).

Reaction of 10α-cholesta-5, 7-dien-3β-ol (5h) with perbenzoic acid

A solution of perbenzoic acid in chloroform (81ml, 0.24M, 19.4m.moles) was added to 10α-cholesta-5, 7-dien -3β-ol (5h; 7.55gm 19.6m.moles) in benzene (300ml) at room temperature. After stirring for two minutes the reaction mixture was washed with aqueous sodium bicarbonate (2x250ml), aqueous sodium carbonate (5x250ml), water (2x250ml), brine (1x250ml) and dried over sodium sulphate. The solvent was removed in vacuo and the crude product product (6.845gm) adsorbed on 5% deactivated alumina (350gm).

Elution with petroleum ether gave a mixture (98mg).

From the NMR data the principal component appeared to have the following spectrum -- δ 4.13 ($W_{h/2}$ 8Hz, CHOH), 3.40, 3.35 (1H); 3.07, 3.02(1H), 1.26 ($C^{19}H_3$), 0.74 ($C^{18}H_3$), 0.825, 0.92 (side chain methyls)ppm.

Elution with benzene-petroleum ether (1:1) gave 5β, 6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c; 3.90gm) as needles (acetone); m.p 79-80.5°; $[\alpha]_D$ + 396° (C 1.02); γ_m 3370, 1688, 1275, 875, 860, 845, 822cm^{-1}; λ_m (cyclohexane) 224nm (ϵ 7300); CD (tetrafluoroethanol), λ_m 219$_{nm}$ ($\Delta\epsilon_m$ + 10.1); ORD (tetrafluoroethanol), $[\phi]_{220}$ + 17800, $[\phi]_{234}$ + 22100 (maxima), $[\phi]_{250}$ + 15600, $[\phi]_{275}$ + 9490, $[\phi]_{350}$ + 4350; NMR, δ 5.42 (d, $J_{C(6)H-C(7)H}$ = 4Hz, C^7H)*, 4.00 ($W_{h/2}$ = 12Hz; C^3-H), 2.81 (d, $J_{C(6)H-C(7)H}$ = 4Hz; C^6H)* 2.475 (d, $J_{C(3)H-C(4)H}$ = 3Hz; C^4H)**, 2.225 (d, $J_{C(3)H-C(4)H}$ = 3Hz; C^4H)***, 1.03 ($C^{19}H_3$), 0.52 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 80.77; H, 11.14%.

Double irradiation experiments.

*Doublets decouple with difference frequency of 156c/s

**Doublet collapses with difference frequency of -94c/s

***Doublet collapses with difference frequency of -105c/s

$C_{27}H_{44}O_2$ requires : C, 80.94; M, 11.07%).

Elution with benzene-petroleum ether (4:1) gave a mixture (619mg) of 5β, 6β-epoxy-5β, 10α-cholest-7-en-3β-ol (72c) and 3β, 6β-oxido-5α, 10α-cholest-7-en-5-ol (71b).

Further elution with benzene-petroleum ether (4:1) and with benzene gave 3β, 6β-oxido-5α, 10α-cholest-7-en-5-ol (71b; 490mg) as blocks (acetone); m.p 126-7°; $[\alpha]_D$ + 60.5 (c 1.03); ν_m 3400, 1685, 1130, 965 cm^{-1}; λ_m (cyclohexane) 207nm (ϵ_m 6760); NMR: δ:5.26 (d, $J_{C(6)H-C(7)H}$ = 5.5Hz; C^7H)*, 4.23 ($W_{h/2}$ = 8Hz; C^3H), 3.74 (d, $J_{C(6)H-C(7)H}$ = 5.5Hz; C^6H)*, 1.05 ($C^{19}H_3$), 0.62 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 80.94; H, 11.10%. $C_{27}H_{44}O_2$ requires: C, 80.94; H, 11.07%).

Elution with ether gave 5β, 10α-cholest-7-en-3β, 5β, 6α-triol (70d; 1.78gm) as needles (pentane); m.p 179-80.5°; $[\alpha]_D$ + 178° (C 1.01); ν_m(CCl_4) 3655 (sharp), 3550 (broad), 1007cm^{-1}; λ_m (cyclohexane) 216$_{nm}$ (ε 3200); NMR, δ 5.34 (d, $J_{C(6)H-C(7)H}$ = 5Hz; C^7H) 4.23 ($W_{h/2}$ = 8Hz, C^3H), 3.74 (d, $J_{C(6)H-C(7)H}$ = 5Hz; C^6H), 1.13 ($C^{19}H_3$), 0.55 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 77.63; H, 11.13%. $C_{27}H_{46}O_3$ requires C, 77.46; H, 11.07%).

From TLC and NMR data of mixed fractions the

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*Double irradiation experiment: Doublets collapse with difference frequency of + 91c/s and -91c/s respectively.

yields of epoxide (72c) and ether (71b) were estimated as 55% and 12% respectively. The yield of triol was 25%.

Hydrolysis of 5β, 6β-epoxy-5β, 10α-cholest-7-en-3β-ol (72c).

The epoxide (72c; 92mg) in ether (5ml) was adsorbed onto active alumina (5gm) and left for 18 hours. Elution with ether gave the epoxide (72c, 2mg). Elution with methanol gave 5β, 10α-cholest-7-ene-3β, 5β, 6α-triol (70d, 85mg), m.p. 179-81, $[\alpha]_D$ + 177°, identical, in spectral properties, to the triol isolated from the crude epoxidation product (P. 141).

Direct Preparation of 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d).

10α-Cholesta-5, 7-dien-3β-ol (5h, 9.7gm) was treated with perbenzoic acid as previously described (P. 139). The crude product (9.5gm) was adsorbed onto active alumina and left for four days. Elution with ether gave 3β, 6β-oxido-5α, 10α-cholest-en-5-ol (71b, 1.3gm), m.p. 125-7°, $[\alpha]_D$ + 66°. Further elution with ether gave a mixture (319mg) of unidentified compounds (TLC). Elution with methanol gave 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d), m.p. 179-80°, $[\alpha]_D$ + 170°.

5β, 10α-cholest-7-ene-3β, 5, 6α-triol 3, 6 diacetate (70e).

A solution of 5β, 10α-cholest-7-ene-3β, 5, 6α-triol

(70d, 104mg) in pyridine (1ml) and acetic anhydride (0.2ml) was left at room temperature for six days and heated on a steam bath for two hours. The crude product was isolated via ether as a gum (pure to TLC); NMR, δ 5.28 ($W_{h/2}$ 9c/s; C^7H and C^3H), 4.99 (d, J = 5c/s; C^6H); 2.075, 2.02 (2 x CH_3-CO_2-) 1.10 ($C^{19}H_3$), 0.60 ($C^{18}H_3$), 0.92 0.82 (side chain methyls)ppm.

5-hydroxy-5β,10α-cholest-7-ene-3,6-dione (77).

Jones reagent was added dropwise to a stirred solution of 5β,10α-cholest-7-ene-3β,5,6α-triol (70d, 105mg) in acetone (2ml). When there was a residual red coloration the excess reagent was quenched by the addition of aqueous sodium bisulfite. The crude product (106mg) isolated via dichloromethane, was adsorbed onto 5% deactivated alumina (10gm).

Elution with benzene-ether (9:1 gave 5-hydroxy-5β,10α-cholest-7-ene-3,6-dione (77; 62mg) as a gum (Pure to TLC); γ_m(smear), 3450, 1715, 1670, 1630cm^{-1}; λ_m(cyclohexane) 245nm (ϵ19670); ORD (cyclohexane), $[\phi]_{257}$ + 29,540 (peak), $[\phi]_{242}$O, $[\phi]_{227}$ -22,790 (trough), a = + 523; CD (cyclohexane), λ_m242nm ($\Delta\epsilon_m$ + 13.34), 305nm ($\Delta\epsilon_m$ - 0.74, shoulder), 339$_{nm}$, 349$_{nm}$ ($\Delta\epsilon_m$ -1.55); NMR, δ 5.73 ($W_{h/2}$ 3Hz; C^7H), 3.12

($W_{h/2}$ 6Hz, removed by D_2O; OH), 2.625 ($W_{h/2}$ 2Hz, C^4H_2), 2.48 ($W_{h/2}$ 2Hz, C^2H_2), 1.18 ($C^{19}H_3$), 0.61 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 78.1; H, 10.3%. $C_{27}H_{42}O_3$ requires: C, 78.2; H, 10.3%).

5β,10α-cholest-7-ene-3β,5-diol (76a)

A solution of 5β,6β-epoxy-5β,10α-cholest-7-en-3β-ol (72c; 155mg) and lithium aluminium hydride (75mg) in dry ether (10ml) was heated under reflux for an hour. The crude product (95mg) was isolated via ether and adsorbed onto 5% deactivated alumina.

Elution with benzene-petroleum ether (4:1) gave 10α-cholest-7-ene-3β,5-diol (76a; 73mg) as needles (acetone); m.p. 126-8°; $[\alpha]_D$ + 139° (c 1.06); γ_m (CCl_4), 3641, 3643, 3561, 1080, 990, 855cm^{-1}; λ_m (cyclohexane) 204nm (ε 5110); NMR: δ 5.05 ($W_{h/2}$ 8Hz; C^7H), 4.05 ($W_{h/2}$ 9Hz; C^3H), 3.22 ($W_{h/2}$ 18Hz, removed by D_20, OH), 0.95 ($C^{19}H_3$), 0.55 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 80.24; H. 11.37%. $C_{27}H_{46}O_2$ requires: C, 80.54; H, 11.52%).

Oxidations of 5β,10α-cholest-7-ene-3β,5-diol (76a) with Jones Reagent.

The diol (76a, 124mg) in dry acetone (10ml) was treated

with Jones reagent in the usual manner (e. g. P.143) and the crude product (120mg) adsorbed onto 5% deactivated alumina.

Elution with benzene gave 5-hydroxy-5β, 10α-cholest-7-en-3-one (76b; 45mg) as a gum (pure to TLC); ν_m(smear), 3540, 1708, 1660cm^{-1}; NMR, δ 5.10 ($W_{h/2}$ 8Hz; C^{7}H), 1.18 (C^{19}H$_3$), 0.53 (C^{18}H$_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: M^+ 400.335027. $C_{27}H_{44}O_2$ requires 400.334113).

Elution with benzene-ether (9:1) gave 5-hydroxy-5β, 10α-cholest-7-en-3, 6-dione (77, 33mg), identical in all respects to the sample prepared from 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d); ref. P. 143.

Jones reagent was added dropwise to a stirred solution of the diol (76a; 96mg) in acetone (2ml) until there was a residual red coloration. After ten minutes stirring the excess reagent was quenched by the addition of aqueous sodium bisulfite. The crude product, isolated via dichloromethane, was adsorbed onto 5% deactivated alumina (10gm). Elution with benzene gave unidentified non-polar material (8mg). Elution with benzene-ether (19:1) gave 10α-cholest-4, 7-diene-3, 6-dione (78; 26mg) as a gum (pure to TLC), ν_m 1690 (C^3=O), 1650

(C^6=O), 1630, 1605 (C=C), 880 cm^{-1}; λ_m (cyclohexane), 306nm (ϵ_m 2864); NMR, δ 6.62 ($W_{h/2}$ 1.5Hz; C^4H), 5.98 ($W_{h/2}$ 2Hz; C^7H), 1.35 ($C^{19}H_3$), 0.53 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: M^+ 396.301895. $C_{27}H_{40}O_2$ requires M^+ 396.302814).

Elution with benzene-ether (9:1) gave 5-hydroxy-5β, 10α-cholest-7-ene-3,6-dione (77; 29mg) identical (NMR, TLC) to a previously characterized sample (P. 143).

Oxidation of 5β, 10α-cholest-7-ene-3β, 5-diol (76a) with chromium trioxide-pyridine complex.

Chromium-trioxide (78mg; 0.78m.mole) was added to a stirred solution of pyridine (0.12ml; 1.56m.mole) in dry dichloromethane. The solution was stoppered and stirred for fifteen minutes producing a deep burgundy color. The diol (76a; 52mg) in dry dichloromethane (0.5ml) was then added. After a further fifteen minutes of stirring the solution was decanted and the tarry residue washed with ether (2x10ml). The combined organic phases were then washed with 5% aqueous sodium hydroxide (3x20ml), 5% aqueous hydrochloric acid (1x20ml), aqueous saturated sodium bicarbonate (20ml) and brine (1x20ml). The solution was dried over magnesium sulphate

and the solvent removed in vacuo. The crude product (46mg) was adsorbed onto 5% deactivated alumina (10gm).

Elution with benzene gave 5-hydroxy-5β, 10α-cholest-7-en-3-one (76b, 32mg) identical, by NMR and IR, to the sample described on P. 143.

Attempted Hydrogenations of 10α-cholest-7-ene-3β, 5, 6α-triol (70d).

1. The triol (70d; 209mg) in dry ethanol (10ml) with Adams catalyst (50mg) was stirred under hydrogen (1atm) for twelve days. The mixture was filtered and the solvent removed in vacuo to gave a crude product consisting mainly of unreacted starting material.

2. The triol (150mg) in glacial acetic acid (10ml) with Adams catalyst was stirred under hydrogen (1 atm) for ten days. The catalyst was removed by filtration and aqueous bicarbonate (30ml) added. Extraction with ether gave the crude product (125ml) which was then adsorbed onto 5% deactivated alumina (10gm).

Elution with benzene-petroleum ether (1:1) gave a mixture (30mg) containing at least two compounds (TLC). The NMR spectra of these fractions showed no downfield protons (i.e. δ 3.0-8.0ppm). Elution with benzene gave 5β, 10α-

cholest-7-ene-3β,5-diol (76a), (30mg), m.p. 125-7°C, $[\alpha]_D$ + 132° identical by TLC and spectral data to a sample prepared by reduction of the epoxide (72c); ref P. 144.

Elution with benzene-ether (9:1) gave 5β,10α-cholest-7-ene-3β,5,6α-triol 6-acetate (70g, 35mg); NMR:δ5.26 (d, J = 5Hz, C^7H), 5.02 (d, J = 5Hz, C^6H), 4.23 ($W_{h/2}$ = 8Hz, C^3H , 2.02 (CH_3CO_2-) 1.10 ($C^{19}H_3$), 0.54 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. Further elution with benzene-ether (9:1) gave a mixture of at least three compounds, (NMR, TLC).

3. The triol (990mg) in glacial acetic acid (80ml) with Adams catalyst (250mg) was stirred under hydrogen for eight days. Saturated bicarbonate (200ml) was then added and the mixture extracted with ether. The crude product (980mg) was adsorbed onto 10% deactivated alumina (50gm).

Elution with petroleum ether gave non-polar fractions (298mg) which appeared, from NMR and TLC data, to contain at least three compounds. Elution with benzene-petroleum ether (1:2 to 1:1) gave a gum (148mg) the major component of which had the following NMR spectral data: δ3.58 (CHOH) 1.00 ($C^{19}H_3$) 0.70 ($C^{18}H_3$) 0.92, 0.83 (side chain methyls)ppm.

Recrystallization from acetone gave a crystalline sample (29mg), m.p. 110-25° raised to 120-5°C by further recrystallization. These crystals gave a positive test to tetranitromethane. (Found: C: 81.8; H, 11.7% $C_{27}H_{46}O_2$ requires: C, 80.54; H, 11.51%).

Elution with benzene-petroleum ether (1:1) gave 5β, 10α-cholest-7-ene-3β, 5-diol (76a, 301mg) contaminated with the above unknown. Identification followed from NMR data; full characterization of this compound is on P. 144. Elution with benzene gave a mixture (101mg) which appeared from NMR and TLC data to consist of at least two components.

Ozonolysis of "unknown" from hydrogenation of 5β, 10α-cholest-7-ene-3β, 5, 6α-triol (70d).

Ozone was bubbled through a solution of the unknown reduction product* (58mg; impure) in chloroform (5ml) at (-40)-(-60)°C** for two hours. The solvent was removed at room temperature in vacuo and the solid material dissolved in acetic acid (5ml). Zinc dust (70mg) was added and the solution stirred for two hours after which time it was diluted with aqueous sodium bicarbonate and extracted with ether. The crude product (53mg) exhibited an absorbtion band at

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*From fractions eluted with benzene-petroleum ether on P.148.

**Dry ice-acetone.

ca 1715cm^{-1} in the infra red-spectrum.

3β, 5-Dihydroxy-5β, 10α-cholest-7-en-6-one (70f)

A solution of 5β, 10α-cholest-7-en-3β, 5, 6α-triol (70d; 996mg) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (1.4gm) in dry benzene (100ml) was stirred at room temperature for seventy two hours. The reaction mixture was then adsorbed onto 10% deactivated alumina (500gm).

Elution with benzene gave 3β, 5-dihydroxy-5β, 10α-cholest-7-en-6-one (70f ; 874mg) as needles (acetone);m.p. 182-3°; $[\alpha]_D$ + 237° (c 1.02); ν_m3510, 3400, 1680, 1630, 865cm^{-1}; λ_m(cyclohexane), 240nm (ϵ_m7600); CD (cyclohexane), λ_m240nm ($\Delta\epsilon_m$ + 14.9), 345nm ($\Delta\epsilon_m$ - 1.63); ORD (cyclohexane) $[\phi]_{400}$ + 1900, $[\phi]_{370}$ + 960, $[\phi]_{350}$ + 3840, $[\phi]_{325}$ + 9830, $[\phi]_{300}$ + 12640, $[\phi]_{285}$ + 15340, $[\phi]_{275}$ + 20380, $[\phi]_{256}$ + 40750 (peak), $[\phi]_{240}$ O, $[\phi]_{225}$ - 16,780 (trough), a + 575; NMR, δ 5.67 ($W_{h/2}$ 3Hz; C^7H), 4.27 ($W_{h/2}$ 8Hz, C^3H), 0.95 ($C^{19}H_3$) 0.63 ($C^{18}H_3$) 0.82, 0.92 (side chain methyls)ppm. (Found : C, 77.94; H, 10.68%, $C_{27}H_{44}O_3$ requires : C, 77.84; H, 10.64%).

6-Oxo-5β, 10α-cholest-7-ene-3β, 5-diol, 3-acetate (70i).

Acetic anhydride (0.2ml) was added to a solution of

3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f; 200mg) in pyridine (2ml) and the mixture left for seventeen hours at room temperature. The crude product (197mg), isolated via ether, gave 6-oxo-5β,10α-cholest-7-ene-3β,5-diol, 3-acetate (70i, 170mg) as plates (ethanol); m.p. 220-1°; ν_m 3560, 1740, 1685, 1630, 1239, 1197, 822cm^{-1}; λ_m (cyclohexane) 241nm (13,900); CD (cyclohexane) λ_m 241nm ($\Delta\epsilon_m$ + 12.63), 342nm ($\Delta\epsilon_m$ - 1.52); ORD (cyclohexane), $[\phi]_{275}$ + 15340, $[\phi]_{260}$ + 35190 (peak), $[\phi]_{240}$ O, $[\phi]_{224}$ - 25260 (trough), $[\phi]_{210}$ - 14440, a = + 604; NMR: δ 5.68 ($W_{h/2}$ 3Hz, C^7H), 5.32 ($W_{h/2}$ 7½Hz, C^3H), 2.07 (CH_3-CO_2-), 0.96 ($C^{19}H_3$), 0.65 ($C^{18}H_3$), 0.82, 0.91 (side chain methyls)ppm. (Found : C, 75.65; H, 10.10%. $C_{29}H_{46}O_4$ requires: C, 75.94, H, 10.11%).

Oxidation of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f).

Jones reagent was added dropwise to a stirred solution of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f; 67mg) in acetone (2ml). As soon as there was a residual red coloration the excess reagent was quenched by the addition of sodium meta-bisulfite. The crude product (69mg) isolated via ether, was adsorbed on 5% deactivated alumina (5gm).

Elution with benzene-ether (1:1) gave 5-hydroxy-5β,

10α-cholest-7-ene-3,6-dione (77; 62mg) as a gum (pure to TLC) identified by NMR and IR (Ref. P.143).

Lithium-ammonia reduction of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f).

3β,5-Dihydroxy-5β,10α-cholest-7-en-6-one (70f; 3.18gm) in dry ether (200ml) was added to a solution of lithium (2gm) in liquid ammonia (ca 150ml distilled off lithium immediately prior to use). After stirring for ten minutes methanol was added and the blue color of the solution discharged. The mixture was then thrown into water and stood at room temperature to allow the ammonia to evaporate. The crude product (2.94gm), isolated, via ether, was adsorbed onto 10% deactivated alumina (500gm).

Elution with benzene-petroleum ether (1:1) gave an unidentified mixture of non-polar compounds (127mg, ca 4%). Elution with benzene gave 3β-hydroxy-5β,8α,10α-cholestan-6-one (84a; 141mg; 4.7%) as needles (ether); m.p. 163-4°; ν_m 1695cm^{-1}; λ_m (MeOH) 283nm, (ε30); CD (McOH), λ_m 280nm ($\Delta\epsilon$ -0.278); ORD (MeOH), $[\phi]_{250}$ + 1845, $[\phi]_{260}$ + 1695, $[\phi]_{270}$ + 1390, $[\phi]_{280}$ + 870, $[\phi]_{290}$ + 450, $[\phi]_{300}$ + 565, $[\phi]_{310}$ + 750, $[\phi]_{320}$ + 720; NMR: δ4.15 ($W_{h/2}$ 7Hz, C^3H),

0.85 ($C^{19}H_3$, $C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: M^+ 402.349762. $C_{27}H_{46}O_2$ requires 402.349815).

Further elution with benzene gave 3β,5-dihydroxy-5β, 8α,10α-cholestan-6-one (84b, 893mg; 30%) as blocks (ether); m.p. 181-2°; $[\alpha]_D$ + 29° (c + 01); ν_m (CCl_4 3640, 3495, 1720, 1026cm^{-1}; λ_m (MeOH) 297nm (ϵ_m40); CD (MeOH), λ_m296nm ($\Delta\epsilon_m$ -0.406); ORD (MeOH), $[\phi]_{250}$ + 2600, $[\phi]_{264}$ + 2640 (peak), $[\phi]_{280}$ + 2280, $[\phi]_{300}$ + 1110, $[\phi]_{314}$ + 200 (trough), $[\phi]_{330}$ + 490, a = -24; NMR, δ 4.30 ($W_{h/2}$ 7Hz; C^3H), 3.52, 3.33, 3.29, 3.11 (1H; C^7H_β), 0.85 ($C^{19}H_3$, $C^{18}H_3$), 0.82, 0.92 (side chain methyls) ppm. (Found: C, 77.73; H, 11.02%. $C_{27}H_{46}O_3$ requires : C, 77.46, H, 11.07%. M^+418.344145; $C_{27}H_{46}O_3$ requires M^+ 418.344676).

Elution with benzene-ether (19:1) gave 5β,10α-cholest-7-ene-3β,5,6β-triol (70h; 94mg; 3.1%) as needles (ether-pentane); m.p. 136-7°; $[\alpha]_D$ + 117° (c 1.02); ν_m 3370, 1680, 995cm^{-1}; NMR, δ 4.95 ($W_{h/2}$ 5Hz, C^7H), 4.13 ($W_{h/2}$ 8Hz, C^3H), 3.82 ($W_{h/2}$ 5½Hz; C^6H), 0.97 ($C^{19}H_3$), 0.56 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 77.30; H, 11.07% M^+ 418.344559. $C_{27}H_{46}O_3$ requires C, 77.46, H, 11.07%; M^+ 418.344676).

Elution with benzene-ether (9:1) gave 5α,10α-cholestane-3β,6α-diol (85a; 401mg; 15.5%) as needles (acetone);

m.p. 160-1°; $[\alpha]_D$ + 42° (c 1.00); ν_m 3400cm^{-1}; NMR. δ 4.08 (2H, $W_{h/2}$ ca 9Hz and $W_{h/2}$ ca 20Hz; C^3H, C^6H), 1.00 ($C^{19}H_3$), 0.65 ($C^{18}H_3$), 0.82, 0.91 (side chain methyls)ppm. (Found: C, 80.23; H, 11.84%. $C_{27}H_{48}O_2$ requires: C, 80.14; H, 11.95%. $M^+ - H_2O$ = 386.354759; $C_{27}H_{48}O_2 - H_2O$ requires 386.354848.)

Further elution with benzene-ether (9:1) gave mixtures of diols 85a and 84e (126mg). Further elution with benzene-ether (9:1) followed by benzene-ether (4:1) gave 5β, 8α, 10α-cholestane-3β, 6β-diol (84e; 885mg) as needles (acetone); m.p. 214-5°; $[\alpha]_D$ + 11° (c 1.02); ν_m 3375cm^{-1}; NMR, δ 4.12 ($W_{h/2}$ 7Hz, C^3H), 3.33 ($W_{h/2}$ ca 20Hz; C^6H), 0.82, 0.92 ($C^{18}H_3$, $C^{19}H_3$; side chain methyls)ppm. (Found: C, 79.63; H, 12.15% $C_{27}H_{48}O_2$ requires - C, 80.13; H, 11.95%)*

DDQ oxidation of 5β, 10α-cholest-7-ene-3β, 5, 6β-triol (70h)

A solution of 5β, 10α-cholest-7-ene-3β, 5, 6β-triol (70h; 84mg) ans 2, 3-dichloro-5, 6-dicyano- 1, 4-benzoquinone (100mg) in dry benzene (15ml) was stirred at room temperature for forty eight hours. The mixture was then adsorbed onto 10% deactivated alumina (200gm). Elution with benzene gave

*Satisfactory analyses were obtained for derivative of this diol.

3β,5-dihydroxy-5β,10α-cholest-7-en-3-one (70f; 69mg), m.p. 181-183°C, $[\alpha]_D$+ 230° identical to the product obtained from the DDQ oxidation of 5β,10α-cholest-7-en-3β,5,6α-triol (70d). (Ref. P.150).

6-Oxo-5β,8α,10α-cholestane-3β,5-diol,3-acetate (84j).

A solution of 3β,5-dihydroxy-5β,8α,10α-cholestan-6-one (84b; 55mg) and acetic anhydride (0.1ml) in pyridine (1ml) was stirred for eighteen hours at room temperature. The crude product (58mg), isolated via ether, gave 6-oxo-5β,8α,10α-cholestane-3β,5-diol, 3-acetate (84j; 48mg) as needles (acetone); m.p. 214-5°; ν_m (CCl_4) 3550 (sharp), 3450 (broad), 1742, 1722, 1240, 1200cm^{-1}; ORD (cyclohexane), $[\phi]_{260}$ + 2830, $[\phi]_{280}$ + 2580, $[\phi]_{300}$ + 1090, $[\phi]_{319}$ + 30, $[\phi]_{340}$ + 520, $[\phi]_{360}$ + 610, a = ca 28; NMR, δ 5.31 ($W_{h/2}$ 7Hz; C^3H), 3.12, 3.30, 3.35, 3.53 (q, 1H, C^7H_β), 3.30 (removed by D_2O shake, -OH), 2.08 (CH_3-CO_2-) 0.85 ($C^{18}H_3$, $C^{19}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found C : 75.69; H, 10.30%. $C_{29}H_{48}O_4$ requires: C, 75.61; H, 10.50%).

5-Hydroxy-5β,8α,10α-cholestane-3,6-dione (84l)

Jones reagent was added dropwise to a stirred solution of 3β,5-dihydroxy-5β,8α,10α-cholestan-6-one (84b; 210mg) in acetone (5ml) until there was a residual red coloration.

Aqueous sodium bisulfite was added and the mixture was extracted with dichloromethane. The crude product adsorbed onto 10% deactivated alumina (10gm). Elution with benzene gave 5-hydroxy-5β, 8α, 10α-cholestane-3, 6-dione (84 l, 143mg) as a gum (pure to TLC); ν_m (smear) 3450, 1710cm^{-1}; NMR, δ, ca 3.17 (multiplet, 2H, C^{7}H and C^{2}H), 1.12 (C^{19}H$_3$), 0.85 (C^{18}H$_3$), 0.92, 0.82 (side chain methyls)ppm. Found M$^+$ 416.329316; $C_{27}H_{43}O_3$ requires M$^+$ 416.329027.

5β, 8α,10α-Cholestane-3β, 5, 6α-triol (84c).

Lithium aluminium hydride (50mg) was added to a solution of 3β, 5-dihydroxy-5β, 8α, 10α-cholestan-6-one (84b; 100mg) in dry ether (20ml) and the mixture was refluxed for two hours. The reaction was quenched by addition of sodium sulphate-dodecahydrate and the steroidal material isolated via ether to yield 5β, 8α, 10α-cholestane-3β, 5, 6α-triol (84c; 96mg) as a gum (pure to TLC). NMR, δ, 4.23 ($W_{h/2}$ 9Hz; C^{3}H), 3.57 ($W_{h/2}$ 6Hz, C^{6}H), 1.17 (C^{19}H$_3$), 0.80 (C^{18}H$_3$), 0.80, 0.90 (side chain methyls)ppm. No elemetal analysis or mass spectral data was obtained but the diacetate (84k) had a satisfactory elemental analysis.

5β, 8α, 10α-Cholestane-3β, 5, 6α-triol 3, 6-diacetate (84k).

A solution of the triol (84c; 88mg) and acetic anhydride (0.1 ml) in pyridine (10ml) was left at room temperature overnight and then heated on a steam bath for two hours. The crude product (102mg), isolated via ether, was adsorbed onto 10% deactivated alumina (10gm).

Elution with benzene gave 5β, 8α, 10α-cholestane-3β, 5, 6α-triol 3, 6-diacetate (84k; 82mg) as blocks (acetone); m.p. 150-2°; ν_m 3600, 3460, 1735, 1250, 1223, 1200, 1190, 1045, 1025cm^{-1}; NMR, δ 5.28 ($W_{h/2}$ 8Hz; C^{3}H), 4.73 ($W_{h/2}$ 4Hz, C^{6}H), 3.25 ($W_{h/2}$ 2Hz, removed by D_2O shake; -OH), 2.07, 2.03 (2 x CH_3-CO_2-), 1.17 (C^{19}H_3), 0.82 (C^{18}H_3), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 73.74; H, 10.52%. $C_{31}H_{52}O_5$ requires C, 73.77; H, 10.38%).

6-Oxo-5β, 8α, 10α-cholestan-3β-yl acetate (84f).

A solution of 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a; 50mg) in acetic anhydride (0.1ml) and pyridine (1ml) was left overnight at room temperature and then heated on a steam bath for two hours. The crude product (61mg) was isolated via ether and adsorbed onto 10% deactivated alumina (5gm). Elution with petroleum ether-benzene (3:1)

gave 6-oxo-5β, 8α, 10α-cholestan-3β-yl acetate (84f; 48mg) as needles (acetone); m.p. 172-3°; ν_m 1740, 1720, 1240cm^{-1}; λ_m (MeOH) 300nm (ϵ 66); CD (MeOH) λ_m 303nm ($\Delta\epsilon_m$ + 0.28); ORD (MeOH) $[\phi]_{320}$ + 890 (peak), $[\phi]_{300}$ + 420, $[\phi]_{289}$ + 170 (trough), a = +7; NMR, δ 5.15 ($W_{h/2}$ 8Hz; C^{3}H), 2.07 (CH_3CO_2-), 0.88 (C^{19}H$_3$, C^{18}H$_3$), 0.92, 0.825 (side chain methyls)ppm. (Found : C, 78.20; H 10.70%. $C_{29}H_{48}O_2$ requires: C, 78.33; H, 10.79% .)

5β, 8α, 10α-Cholestane-3, 6-dione (84g).

A mixture of chromium trioxide (AR, 65mg), pyridine (dry, 0.05ml) and dichloromethane (dry, 1.5ml) was stirred in a stoppered flask for fifteen minutes producing a deep burgundy colored solution. 3β-Hydroxy-5β, 8α, 10α-cholestan-6-one (84a; 37mg) in dichloromethane (0.5ml) was then added and stirring continued for a further fifteen minutes. The solution was decanted and the tarry residue washed with ether. The combined organic phases were washed with 5% aqueous NaOH (3x20ml), 5% aq HCl (1x20ml), aq saturated $NaHCO_3$ (1x20ml), brine (1x20ml). After drying over magnesium sulphate the solvent was removed in vacuo and the crude product (40mg) adsorbed onto 10% deactivated alumina (5gm).

Elution with benzene-petroleum ether (1:1) gave 5β, 8α, 10α-cholestane-3, 6-dione (84g; 23mg) as needles (MeOH); m.p. 145-6°; ν_m 1710cm^{-1}; λ_m(MeOH) 285nm (ε 41); CD (MeOH) λ_m285nm ($\Delta\epsilon_m$ - 1.26); ORD (MeOH), $[\phi]_{225}$ + 4320, $[\phi]_{250}$ + 4870, $[\phi]_{262}$ + 5650 (peak), $[\phi]_{275}$ + 4480, $[\phi]_{297}$ O, $[\phi]_{306}$ = 825 (trough), $[\phi]_{330}$ O, $[\phi]_{400}$ + 310, a + -65; NMR, δ 1.08 ($C^{19}H_3$), 0.83 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls) ppm. (Found: C, 80.57; H, 11.20%. $C_{27}H_{44}O_2$ requires: C, 80.94 H, 11.07%. M^+400.334850; $C_{27}H_{44}O_2$ requires M^+400.334113).

Attempted Isomerizations of 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a) and the 3β-acetoxy- (84f) and 3-oxo- (84g) derivatives.

3β-Hydroxy-5β,8α,10α-cholestan-6-one (84a; 6mg) was adsorbed onto active alumina (2gm) and left overnight. Elution with ethanol-ether (1:9) gave a gun (6mg); NMR, δ 0.90, 0.82ppm (angular and side chain methyls). The methylene envelope was identical to that of the starting material. TLC also indicated that no change had occured.

5β, 8α, 10α-Cholestane-3, 6-dione (84g; 33mg) was adsorbed onto active alumina (5gm) and left overnight. Elution with ether-methanol (9:1) gave unchanged dione (30mg), as

a gum, identified by NMR, IR and TLC. A small analytical sample recrystallized from methanol had m.p. 144-6°.

6-Oxo-5β, 8α, 10α-cholestan-3β-yl acetate (84f, 30mg) was adsorbed onto active alumina and left overnight. Elution with ether gave a gum (31mg) which was adsorbed onto 10% deactivated alumina (5gm). Elution with ether-pentane (1:19) gave a gum (24mg). The NMR spectrum showed no detectable difference from that of the starting material. A sample recrystallized from acetone had m.p. 171-3 and mixed m.p. (with dione 84g) of 171-3°.

5β, 8α, 10α-Cholestane-3β, 6α-diol (84i).

Lithium aluminium hydride (30mg) was added to a solution of 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a; 48mg) in dry ether (10ml). After heating at reflux for an hour the reaction was quenched by addition of sodium sulphate-dodecahydrate. Isolation of the steroidal material via ether gave 5β, 8α, 10α-cholestane-3β, 6α-diol (84i; 47mg) as a gum (pure to TLC); NMR, δ 4.17 ($W_{h/2}$ 7Hz, $C^{3}H$), 3.72 ($W_{h/2}$ 6Hz; $C^{6}H$), 1.12 ($C^{19}H_3$) 0.77 ($C^{18}H_3$) 0.82, 0.92 (side chain methyls) ppm. Analytical and mass spectral data was obtained for the diacetate (84h), below.

5β, 8α, 10α-Cholestane-3β, 6α-diol diacetate (84h).

A solution of 5β, 8α, 10α-cholestane-3β, 6α-diol (84i, 33mg) in acetic anhydride (0.1ml) and pyridine (10ml) was left at room temperature overnight and heated for two hours on a steam bath. The crude product was isolated via ether and adsorbed onto 10% deactivated alumina (5gm).

Elution with petroleum ether-benzene (4:1) gave 5β, 8α, 10α-cholestane-3β, 6α-diol diacetate (84h; 27mg) as needles (acetone), m.p. 124-5°; ν_m 1742, 1250, 1240, 1230, 1215, 1200cm^{-1}; NMR; δ 5.08 ($W_{h/2}$ 6Hz; C^{3}H), 4.84 ($W_{h/2}$ 5Hz; C^{6}H), 2.05, 2.02 (2 x CH_3CO_2-), 1.11 (C$^{19}H_3$) 0.78 (C$^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found (M^+-60): 428.366817; $C_{29}H_{48}O_2$ requires : 428.365412. Found : C, 76.06, H, 10.65%. $C_{31}H_{52}O_4$ requires C, 76.18; H, 10.72%.

Acetylations of 5β, 8α, 10α-cholestane-3β, 6β-diol (84e).

1. A solution of the diol (84e; 210mg, 0.52m. mole) and acetic anhydride (0.1ml) in pyridine (10ml) was left at room temperature for twenty four hours. The crude product (242mg) was isolated via ether and adsorbed onto 10% deactivated alumina (25gm).

Elution with benzene-petroleum ether (1:4) gave 5β,

8α, 10α-cholestane-3β, 6β diol diacetate (84m; 152mg; 0.31m. mole) as blocks (ethanol); m.p. 157-8°; $[\alpha]_D$ - 38° (C 1.07); ν_m 1730, 1250, 1230, 1220cm^{-1}; NMR, δ 5.05 ($W_{h/2}$ 8Hz; C^{3}H), 4.78, 4.70, 4.61, 4.53, 4.45, 4.37 (C^{6}H), 2.05, 2.00 (2x CH_3CO_2-), 0.98 (C$^{19}H_3$), 0.80 (C$^{18}H_3$) 0.90, 0.80 (side chain methyls)ppm. (Found : C, 76.08; H, 10.72%. $C_{31}H_{52}O_4$ requires : C, 76.18; H, 10.72%).

Elution with benzene-petroleum ether (2:3) gave 5β, 8α, 10α-cholestane-3β, 6β-diol 6-acetate (84n; 76mg; 0.170m. mole) as a gum (pure to TLC); NMR, δ 4.82, 4.73, 4.65, 4.57, 4.48, 4.40 (C^{6}H), 4.09 ($W_{h/2}$ 8Hz; C^{3}H), 2.02 (CH_3CO_2-), 0.97 (C$^{19}H_3$), 0.78 (C$^{18}H_3$), 0.81, 0.90 (side chain methyls). (Found : C, 75.20; H, 10.85%. $C_{29}H_{50}O_3$ requires : C 75.28; H, 10.89%).

2. A solution of the diol (84e; 880mg; 2.17m. mole) in acetic anhydride (1ml) and pyridine (5ml) was left overnight at room temperature and then heated for two hours on a steam bath. The crude product was isolated via ether and recrystallized from ethanol to give the diacetate (84m, 1.013gm; 2.07m. mole) as blocks; m.p. 157-8°, $[\alpha]_D$ - 36° (c 1.02).

3-Oxo-5β, 8α, 10α-cholestan-6β-yl acetate (84o).

A mixture of chromium trioxide (A. R. ; 200mg), dry pyridine (0. 15ml) and dry dichloromethane (3ml) was stirred in a stoppered flask for fifteen minutes producing a deep burgundy-red solution. A solution of 5β, 8α, 10α-cholestane-3β, 6β-diol 3 acetate (84n; 60mg) in dichloromethane (0. 5ml) was added and stirring was continued for a further fifteen minutes. The solution was then decanted and the tarry residue washed with ether (2x50ml). The combined organic phases were washed with 5% aqueous sodium hydroxide (3x20ml), 5% aqueous hydrochloric acid (1x20ml), saturated aqueous sodium bicarbonate (1x20ml), brine (1x20ml) and then dried over magnesium sulphate. Removal of the solvent in vacuo yielded 3-oxo-5β, 8α, 10α-cholestan-6β-yl acetate (84o; 58mg) as needles (acetone); m.p. 158-9°; ν_m 1740, 1720, 1240cm^{-1}; λ_mMeOH) 288nm (ε 13); CD (MeOH) λ_m 288nm (Δε -0. 48); ORD (MeOH), $[\phi]_{250}$ + 710, $[\phi]_{260}$ + 750, $[\phi]_{270}$ + 800 (peak), $[\phi]_{280}$ + 490, $[\phi]_{289}$ O, $[\phi]_{300}$ - 660, $[\phi]_{307}$ - 930 (trough), $[\phi]_{320}$ - 750, $[\phi]_{350}$ - 310, a = -16. 8; NMR, δ 4. 53, 4. 62, 4. 70, 4. 78, 4. 87, 4. 95 (C^{6}H); 2. 03 (CH_3CO_2-), 1. 20(C^{19}H$_3$), 0. 78 (C^{18}H$_3$), 0. 81, 0. 91 (side chain methyls)ppm. (Found: C, 78. 34; H, 10.81%. $C_{29}H_{48}O_3$

requires : C 78.33; H, 10.88%).

Oxidation of 5β, 8α, 10α-cholestane-3β, 6β-diol (84e)

Jones reagent was added dropwise to a stirred solution of the diol (84e; 90mg) in acetone (5ml) until there was a residual red coloration. The excess reagent was then quenched with aqueous sodium bisulfite and the mixture was extracted with chloroform. The crude product (86mg) was adsorbed onto 10% deactivated alumina (10gm). Elution with benzene gave 5β, 8α, 10α-cholestane-3, 6-dione (84g, 45mg) as needles (methanol), m.p. 144-6°, m.m.p. 144-6° identical to the sample obtained from the chromium trioxide-pyridine oxidation of 3β-hydroxy-5β, 8α, 10α-cholestan-6-one (84a; Ref. P.158.

A mixture of chromium trioxide (A.R. 100mg), pyridine (0.1ml) and dichloromethane (dry; 3ml) was stirred in a stoppered flask for fifteen minutes producing a deep burgundy-red colored solution. A solution of the diol (84e; 100mg) in dichloromethane (0.5ml) was added and the mixture stirred for another fifteen minutes. It was then decanted and the tarry deposits washed with ether (2x25ml). The combined organic phases were washed with 5% aqueous sodium hydroxide (3x10ml), 5% aqueous hydrochloric acid (1x10ml) and brine (1x10ml); dried over magnesium sulphate

and the solvent was removed in vacuo to give 5β, 8α, 10α-cholestane-3, 6-dione (84g; 84mg) as needles (EtOH), m.p. 143-5°C.

Acetylation of 5α, 10α-cholestane-3β, 6α-diol (85a).

A solution of the diol (85a; 212mg) in acetic anhydride (0.25ml) and pyridine (2ml) was left at room temperature for twenty four hours. The crude product (140mg), isolated via ether, was adsorbed onto 10% deactivated alumina (20gm). Elution with benzene gave 5α, 10α-cholestane-3β, 6α-diol diacetate (85f; 170mg) as a gum (pure to TLC); NMR, δ 5.22 (multiplet, C^6H), 5.00 ($W_{h/2}$ 8Hz; C^3H), 2.02, 1.98 (2x CH_3CO_2-), 1.05 ($C^{19}H_3$), 0.68 ($C^{18}H_3$), 0.825, 0.92 (side chain methyls)ppm. (Found C, 76.09; H10.79%. $C_{31}H_{54}O_4$ requires : C, 76.18; H, 11.72%).

Further elution with benzene gave 5α, 10α-cholestane-3β, 6α-diol 6-acetate (85e; 76mg) as blocks (acetone); m.p. 134-5°; $[\alpha]_D$ + 81° (C 1.00); ν_m 3375, 1715, 1255 (sharp)cm^{-1}; NMR, δ 5.30, 5.38, 5.48, 5.57, 5.67, 5.75 (C^6H), 4.02 ($W_{h/2}$ 7Hz; C^3-H), 2.06 (CH_3-CO_2-), 1.02 ($C^{19}H_3$), 0.64 ($C^{18}H_3$), 0.82, 0.90 (side chain methyls)ppm. (Found: C, 78.00 ; H, 11.42%. $C_{29}H_{50}O_3$ requires : C, 77.97; H, 11.28%).

3-Oxo-5α, 10α-cholestan-6α-yl acetate (85g).

5α, 10α-Cholestane-3β, 6α-diol, 6 acetate (85e, 68mg) was dissolved in acetone (AR. 5ml) and Jones reagent was added dropwise, with stirring, until there was a residual red coloration. Aqueous sodium bisulfite was then added and the steroidal material isolated via chloroform. The crude product (70mg) in acetone was filtered through 10% deactivated alumina and recrystallized from ether-pentane to give 3-oxo-5α, 10α-cholestan-6α-yl acetate (85g; 18mg) as needles; m.p. 152-3°; ν_m 1725, 1230 (sharp), 1710cm^{-1}; λ_m (MeOH) 293nm (ε24); CD (MeOH) λ_m 293nm ($\Delta\epsilon_m$ +0.28); ORD (MeOH), $[\phi]_{250}$ + 1750, $[\phi]_{273}$ + 1290 (trough), $[\phi]_{306}$ + 2050 (peak), $[\phi]_{325}$ + 1650, $[\phi]_{350}$ + 1250, $[\phi]_{375}$ + 1070, $[\phi]_{400}$ + 845, a + 7.6: NMR, δ 4.35, 4.42, 4.53, 4.61, 4.72, 4.78 (C^6H), 2.025 (CH_3CO_2-), 1.28 ($C^{19}H_3$), 0.65 ($C^{18}H_3$), 0.82, 0.91 (side chain methyls)ppm. (Found : (M^+-60) 384.338123; $C_{29}H_{48}O_3$ requires (M^+-60) : 348.339199).

Oxidation of 5α, 10α-cholestane-3β, 6α-diol (85a).

1. Jones reagent was added dropwise to a stirred solution of the diol (85a, 145mg) in acetone (10ml) until there was a residual red coloration. Aqueous sodium bisulfite was added and the steroidal material isolated via dichloromethane.

The crude product (145mg), in ether, was filtered through 10% deactivated alumina to yield 5α, 10α-cholestane-3, 6-dione (85h; 130mg) as needles (ether-pentane); m.p. 164-5°; ν_m 1728cm^{-1}; λ_m (MeOH) 288nm (ε 55); CD (MeOH), λ_m 293nm (Δε -1.38); ORD (MeOH), $[\phi]_{240}$ + 8010, $[\phi]_{260}$ + 6420, $[\phi]_{273}$ + 6920 (peak), $[\phi]_{296}$ O, $[\phi]_{313}$ - 4650 (trough), $[\phi]_{340}$ -1190, a -116; NMR, δ 1.35 ($C^{19}H_3$), 0.65 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found : C, 80.6; H, 10.9%. $C_{27}H_{44}O_2$ requires : C, 80.94; H, 11.10%).

2. A mixture of chromium trioxide (AR, 220mg), dry pyridine (0.18ml) and dry dichloromethane (6ml) was stirred for fifteen minutes producing a burgundy-red solution. The diol (85a; 100mg), in dichloromethane (0.5ml), was added and stirring continued for a further fifteen minutes. The solution was decanted and the tarry deposits washed with ether (2x20ml). The combined organic phases were washed with 5% aqueous sodium hydroxide (3x20ml), 5% aqueous hydrochloric acid (1x20ml) and brine (1x20ml), and tried over magnesium sulfate. Removal of the solvent in vacuo gave 5α, 10α-cholestane-3, 6-dione (85h), m.p.

163-5°, identical to the sample prepared by Jones oxidation (above).

Attempted isomerization of 5α,10α-cholestane-3,6-dione (85h).

The dione (85h; 61mg) in ether was adsorbed onto active alumina (5gm) and left for twenty hours. Elution with ether-methanol gave unchanged dione (85h; 57mg) identified by NMR, CD and melting point.

7α,8α-Epoxy-5β,10α-cholestan-3β-ol (100).

Metachloroperbenzoic acid (4.8gm) in dry ether (240ml) was added to 5α,10α-cholest-7-en-3β-ol (65c; 4.8gm) in dry ether (240ml). After standing at room temperature for three days the reaction mixture was washed with aqueous sodium bicarbonate (2x250ml), aqueous sodium carbonate (2x250ml), water (1x250ml), and brine (1x250ml), dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product (4.379gm) was adsorbed onto 10% deactivated alumina (300gm). Elution with petroleum ether-benzene(4:1) gave an unidentified mixture, (74mg). Elution with benzene-petroleum ether (3:7) gave 7α,8α-epoxy-5β,10α-cholestan-3β-ol (100; 3.76gm) as fine needles (petroleum ether); m.p. 109-110°; ν_m 3450, 1250, 920, 910, 880, 865, 840cm^{-1}; NMR, δ 3.98 ($W_{h/2}$ 7Hz; C^3H), 3.22 (J = 4Hz, C^7H), 1.07 ($C^{19}H_3$),

0.725 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found : C, 80.53; H, 11.57%. $C_{27}H_{46}O_2$ requires: C, 80.54; H. 11.52%).

Elution with petroleum ether-benzene (2:3) gave a mixture (404mg) of at least three compounds (TLC). This was adsorbed onto 10% deactivated alumina (30gm). Elution with petroleum ether-benzene (3 : 2) gave a gum (155gm); ν_m 3450, 1000cm^{-1}; NMR, δ 4.23 (1H; $W_{h/2}$ 9Hz), 3.18, 3.10, 3.02, 2.93 (2H; J_{AB} = 5Hz), 1.05 (C^{19}-H_3), 0.73 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. Reduction of this gum with lithium aluminium hydride gave an intractable mixture. Relative to that of the starting material the NMR showed a broader and larger signal at δ4.2ppm and the quartet at δ3.06 was greatly reduced. A small scale (5mg) BF_3:Et_2O rearrangement of the gum gave at least four products (TLC).

Boron trifluoride-etherate* catalysed rearrangements of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100).

1. Small scale trials: Solutions of the epoxide (100, 20mg) in ether (2ml) and benzene (2ml) were treated

*The boron trifluoride—etherate complex was distilled several times including once immediately before use. The fraction boiling at 125.5-126°C was used.

with a drop of BF_3— etherate and the reactions followed by TLC. The reaction in benzene was essentially complete in one minute and that in ether in five minutes. Neither showed any further change over a period of three days.

2. Rearrangement in ether. Freshly distilled boron trifluoride-etherate (0.1ml) was added to a solution of the epoxide (100, 105mg) in dry ether (10ml) in a stoppered flask. After ten minutes the mixture was diluted with ether (30ml), washed with aqueous sodium bicarbonate (3x25ml) and brine (1x25ml), dried over sodium sulphate and the solvent removed in vacuo. The crude product (103mg) was adsorbed onto 10% deactivated alumina (10gm).

Elution with benzene-petroleum ether (1:1) gave 3β-hydroxy-5β, 10α-cholestan-7-one (104a; 99mg) as a gum (pure to TLC); ν_m (smear) 3440, 1710cm^{-1}; CD (MeOH), λ_m291 ($\Delta\epsilon_m$ + 2.99); ORD (MeOH), $[\phi]_{240}$ - 2625, $[\phi]_{270}$ -3970 (trough), $[\phi]_{293}$ O, $[\phi]_{309}$ + 3380 (peak), $[\phi]_{330}$ + 1690, $[\phi]_{375}$ + 640, a + 73.5; NMR, δ 4.05 ($W_{h/2}$ 7Hz; C^3H), 0.84 ($C^{19}H_3$), 0.68 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Measured: M^+ = 402.349354. $C_{27}H_{46}O_2$ requires 402.349762.

3. Rearrangement in dimethyl formamide. Freshly distilled boron trifluoride:etherate (0.1ml) was added to a solution of the epoxide(100; 100mg) in dimethyl formamide (4ml) in a stoppered flask. After four hours at room temperature the mixture was diluted with ether (20ml); washed with 5% aqueous sodium bicarbonate (3x20ml) water (3x20ml) and brine (20ml); and dried over magnesium sulphate. The solvent was removed, in vacuo, to yield 3β-hydroxy-5β,10α-cholestan-7-one (104a, 89mg) as a gum; identical by NMR, TLC and IR to the sample characterized above.

7-Oxo-5β, 10α-cholestan-3β-yl acetate (104b).

A solution of 3β-hydroxy-5β,10α-cholestan-7-one (104a; 30mg) in acetic anhydride (0.05ml) and pyridine (0.5ml) was left at room temperature for twenty four hours. The steroidal material was isolated via ether and recrystallized from acetone to yield 7-oxo-5β,10α-cholestan-3β-yl acetate (104b; 35mg) as needles; m.p. 113-4°; ν_m 1740, 1720, 1250 (shoulder), 1235, 1225 (shoulder) cm^{-1}; λ_m(MeOH) 290nm (ε53); CD (McOH), λ_m 292nm ($\Delta\epsilon_m$ + 2.66); ORD (MeOH), $[\phi]_{245}$ -3130, $[\phi]_{270}$ -5455 (trough), $[\phi]_{293}$ O, $[\phi]_{310}$ + 5090 (peak), $[\phi]_{325}$ + 3590, $[\phi]_{375}$ + 1000, a = +105; NMR, δ

5.00 ($W_{h/2}$ 7Hz; $C^{3}H$), 2.08 (CH_3CO_2-), 0.85 ($C^{19}H_3$), 0.70 ($C^{18}H_3$), 0.80, 0.90 (side chain methyls)ppm. (Found: C, 78.10; H, 10.89%. $C_{29}H_{48}O_3$ requires: C, 78.33; H, 10.88%).

5β,10α-Cholestane-3,7-dione (104c).

Jones reagent was added dropwise to a stirred solution of 3β-hydroxy-5β,10α-cholestan-7-one (104a, 40mg) in acetone (5ml) until there was a residual red coloration. Aqueous sodium metabisulfite was added and the mixture extracted with ether. The crude product (44mg), in ether, was filtered through 10% deactivated alumina to give 5β,10α-cholestane-3,7-dione (104c; 39mg) as needles (acetone); m.p. 169-70°; ν_m 1710cm^{-1}; λ_m (MeOH), 286nm (ε50); CD (MeOH) λ_m 294nm ($\Delta\epsilon_m$ + 2.02); ORD (MeOH), $[\phi]_{250}$ -2400, $[\phi]_{273}$ - 4030 (trough), $[\phi]_{294}$ O, $[\phi]_{312}$ + 4130 (peak), $[\phi]_{325}$ + 3300, $[\phi]_{375}$ + 880, $[\phi]_{400}$ + 720, a + 82; NMR, δ 1.10($C^{19}H_3$), 0.67 ($C^{18}H_3$), 0.83, 0.92 (side chain methyls)ppm. (Found: C, 80.72, H, 11.18%. $C_{27}H_{44}O_2$ requires: C, 80.94; H, 11.07%).

Perchloric acid catalyzed rearrangement of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100).

Perchloric acid (aq, 0.1ml, 6%) was added to a solution of the epoxide (100; 100mg) in acetone-water (5:1; 12ml). After eighteen hours at 20° the mixture was diluted with 5% aqueous sodium carbonate (50ml) and extracted with dichloromethane (2x20ml) to give the crude product (100mg) which was then adsorbed on 10% deactivated alumina (10gm). Elution with petroleum ether and petroleum ether-benzene (9:1) gave unidentified non polar material (11mg). Elution with petroleum ether-benzene (7:3) gave 3β-hydroxy-5β, 10α-cholestan-7-one (104a, 81mg) as a gum (pure to TLC), identical by NMR, TLC, IR to other samples (Pp.170-1). Acetylation of this product gave 7-oxo-5β, 10α-cholestan-3β-yl acetate (104b, 35mg) as needles; m.p. 112-14°; m.m.p. 112-4°.

Reaction of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100) with Formic acid.

Formic acid (10ml) was added to a solution of the epoxide (100, 68mg) in ether (5ml). After four hours at 40-50° the mixture was diluted with water (20ml) and washed with chloroform (2x20ml). The combined organic phases were then washed with saturated aqueous bicarbonate (2x20ml)

brine (1x20ml), dried over sodium sulphate and the solvent removed in vacuo. The crude product (79mg) was filtered through 10% deactivated alumina (2ml) to give 7-oxo-5β,10α-cholestan-3β-yl formate (104d; 64mg) as a gum (pure to TLC); ν_m 1725, 1710, 1188cm^{-1}; NMR, δ 8.08 (HCO_2-), 5.20 ($W_{h/2}$ 7Hz, C^3H), 0.85 ($C^{19}H_3$), 0.68 ($C^{18}H_3$), 0.80, 0.90 (side chain methyls)ppm.

Hydrolysis of 7-oxo-5β,10α-cholestan-3β-yl formate (104d).

A solution of 7-oxo-5β,10α-cholestan-3β-yl formate (104d; 56mg) and sodium hydroxide (50mg) in methanol-water (10:1; 22ml) was heated at reflux under nitrogen for half an hour. It was then diluted with sulfuric acid (50ml, 1%) and the steroidal material was isolated via ether. The crude product (50mg) was filtered through 10% deactivated alumina (5gm) to give 3β-hydroxy-5β,10α-cholestan-7-one (104a; 47mg) as a gum (pure to TLC); identified by NMR (Ref. P.170). Acetylation of the gum gave 7-oxo-5β,10α-cholestan-3β-yl acetate (104b; 55mg) as needles (acetone); m.p. 112-4°; m.m.p. 112-4°; identical by NMR and TLC to a previously characterized sample (Ref. P. 171).

Attempted reductions of 7α,8α-epoxy-5β,10α-cholestan-3β-ol (100).

1. Lithium aluminium hydride (20mg) was added to a solution of the epoxide (100; 20mg) in dry ether (10ml) and

the mixture heated at reflux for two hours. It was then quenched by the addition of sodium sulfate-decahydrate, diluted with ether, and filtered through 10% deactivated alumina (2gm). Removal of the solvent, in vacuo, gave a gum (18mg) identified by NMR, TLC as the starting material.

2. Lithium aluminium hydride (20mg) was added to a solution of the epoxide (100; 50mg) in dry tetrahydrofuran (10ml), and the mixture was heated at reflux for a day. The reaction was quenched by the addition of sodium sulfate-decahydrate, diluted with ether (50ml), and filtered through 10% deactivated alumina (2ml) to yield unchanged starting material as a gum (48mg) identified by NMR, TLC.

Reduction of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100)

Lithium (35mg) was added to ethylamine (10ml) and the mixture stirred until it went a deep blue color. The epoxide (100, 50mg; 0.125 m.mole) was then added and stirring was continued for an hour. The mixture was tossed into water, the ethylamine allowed to evaporate, and the steroidal material isolated via ether.

A solution of the crude product (50mg) in acetic anhydride (0.1ml) and pyridine (1ml) was left overnight at

room temperature and then heated for an hour on a steam bath. The steroidal material (52mg) was isolated via ether and adsorbed onto 5% deactivated alumina (5gm). Elution with petroleum ether and petroleum ether-benzene (4:1) gave non-polar material (6mg). Elution with petroleum ether-benzene (7:3 and 3:2) gave 5β,10α-cholestane-3β,7α-diol diacetate (112a; 30mg; 0.0615m.mole; ca 50%) as needles (ethanol); m.p. 133-4°; ν_m 1735, 1230, 1240 (shoulder)cm^{-1}; NMR, δ 5.38 (multiplet; C^7H), 5.00 ($W_{h/2}$ 7Hz; C^3H), 2.06, 2.00 (2 x CH_3CO_2-), 0.97 ($C^{19}H_3$), 0.83 ($C^{18}H_3$), 0.83, 0.91 (side chain methyls)ppm. (Found: C, 76.37; H, 10.51%. $C_{31}H_{52}O_4$ requires : C, 76.18; H, 10.72%).

Elution with petroleum ether-benzene (3:2) gave 5β,10α-cholestane-3β,8α-diol, 3-acetate (113a; 10mg; 0.0224m.mole; 18%) as needles (ethanol); m.p. 119-21°; ν_m 3450, 1730, 1250, 1240, 1230cm^{-1}; NMR, δ 5.03 ($W_{h/2}$ 8Hz; C^3H), 2.07 (CH_3CO_2-), 0.82 ($C^{19}H_3$), 0.725 ($C^{18}H_3$), 0.82, 0.92 (side chain methyls)ppm. (Found: C, 77.8; H, 11.2%. $C_{29}H_{50}O_3$ requires : C, 77.97; H, 11.28%.

Reduction of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f) with sodium borohydride in pyridine.

Sodium borohydride (50mg) was added to a solution of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f; 100mg) in dry pyridine (3ml) and the mixture was stirred at room temperature for seventy two hours. It was then diluted with water (100ml) and extracted with ether (100ml). The ether phase was washed with 2% hydrochloric acid (10 x 50ml), saturated aqueous sodium bicarbonate (3x50ml), and brine (2 x 50ml); dried over sodium sulfate; and the solvent removed in vacuo. The crude product (106mg) was adsorbed onto 10% deactivated alumina (20gm). Elution with benzene - petroleum ether (1:1) gave non polar material (10mg). Elution with benzene-ether (19:1) gave unreacted starting material (70f; 66mg), m.p. 181-3°, identified by NMR and IR. Elution with benzene-ether (1:1) gave 5β,10α-cholest-7-en-3β,5,6α-triol (70d; 14mg), m.p. 178-80°, identified by NMR and IR.

Attempted hydrogenation of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f).

A solution of 3β,5-dihydroxy-5β,10α-cholest-7-en-6-one (70f, 100mg) and Adams catalyst (6mg) in ethanol

(10ml) was stirred under hydrogen (latm) for a week. The mixture was filtered through celite and the solvent removed in vacuo to give unreacted starting material (96mg); m.p. 178-80°; $[\alpha]_D$ + 160°.

Attempted cleavage of 7α, 8α-epoxy-5β, 10α-cholestan-3β-ol (100) on active alumina.

The epoxide (100; 300mg), in benzene, was adsorbed onto active alumina (50gm) and left overnight. Elution with benzene-ether (9:1) gave unchanged starting material (286mg), m.p. 108-10°; identified by NMR and TLC. Further elution with the same solvent gave a mixture (18mg), approximately 1:1 by TLC, of starting material and another compound. The infra-red spectrum of this fraction exhibited a maxima at 1710cm^{-1}.

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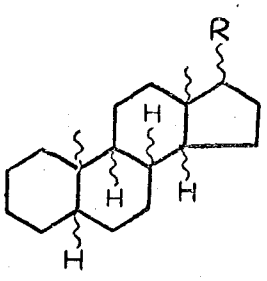

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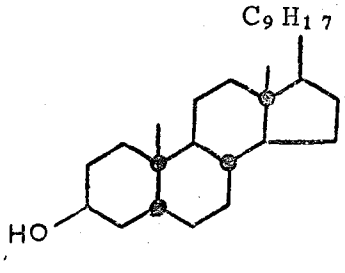

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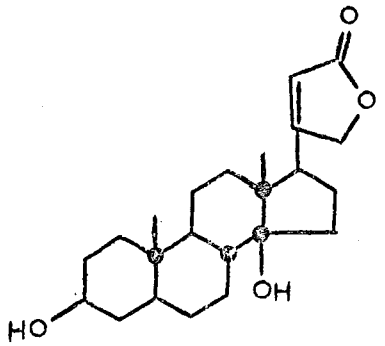

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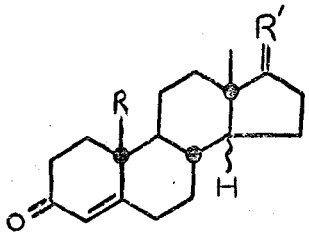
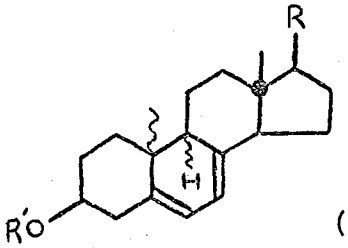


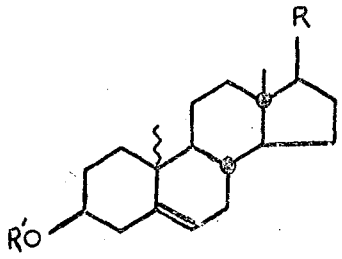
4

	R	R'	C(14)
(a)	H	αCH$_3$C(0)-	β
(b)	Me	βCH$_3$C(0)-	α
(c)	Me	αCH$_3$C(0)-	β
(d)	Me	βC$_8$H$_{17}$	α

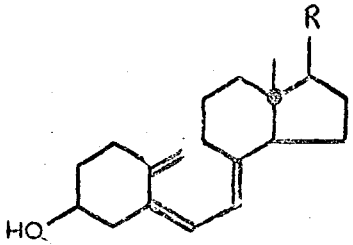


(5)

	R	R'	C(9)	C(10)
5(a)	C$_9$H$_{17}$	H	α	β
5(b)	"	"	β	α
5(c)	"	"	α	α
5(d)	"	"	β	β
5(e)	"	Ac	β	β
5(f)	C$_8$H$_{17}$	H	α	β
5(g)	"	"	β	α
5(h)	"	"	α	α
5(i)	"	"	β	β
5(j)	"	Ac	α	β
5(k)	CH$_3$C(0)-	H	α	β
5(l)	CH$_3$C(0)-	H	β	α
5(m)	C$_8$H$_{17}$	Ac	α	α
5(n)	C$_9$H$_{17}$	Ac	α	α

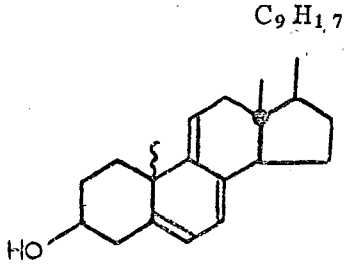


	R	R'	C(10)
6(a)	C$_8$H$_{17}$	H	β
6(b)	"	H	α
6(c)	OAc	Ac	β



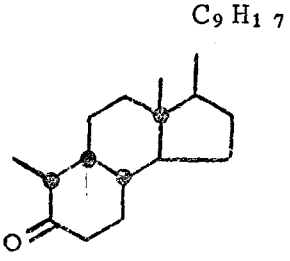
7(a) R = C$_9$H$_{17}$

7(b) R = C$_8$H$_{17}$



8(a) 10β

8(b) 10α



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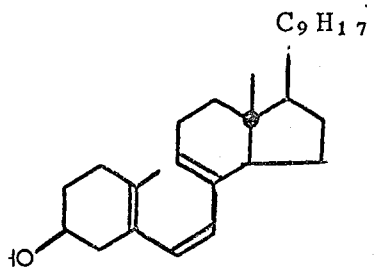

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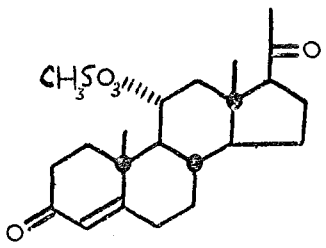

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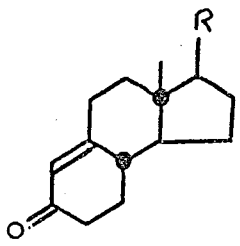
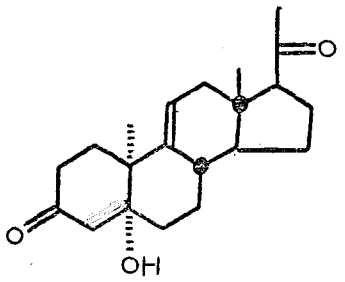


12(a) R = $CH_3C(O)-$

12(b) R = C_8H_{17}



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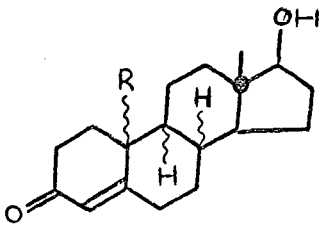
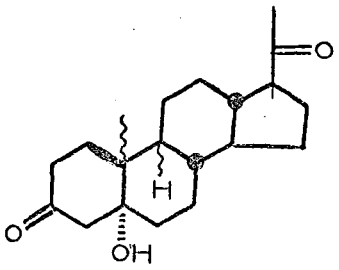
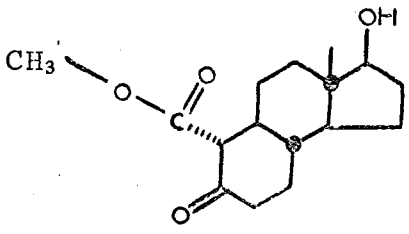


	C(8)	C(9)	R
15(a)	β	α	βMe
15(b)	β	α	αCH_2OH
15(c)	β	α	αMe
15(d)	β	α	αH
15(e)	β	β	βMe
15(f)	β	β	αMe
15(g)	β	β	βH
15(h)	β	α	αH
15(i)	β	β	αH
15(j)	β	α	βH
15(k)	α	α	αH
15(l)	α	α	βMe



14(a) 9α,10α

(b) 9β,10α



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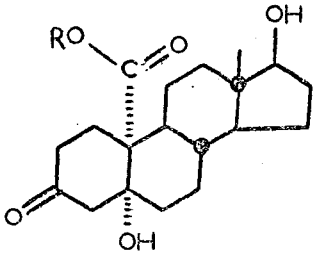
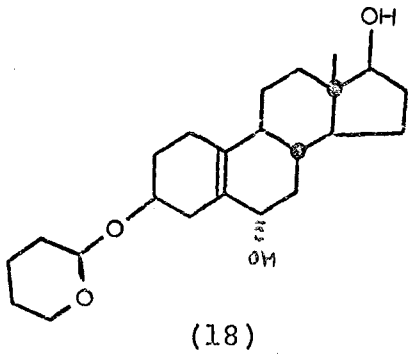
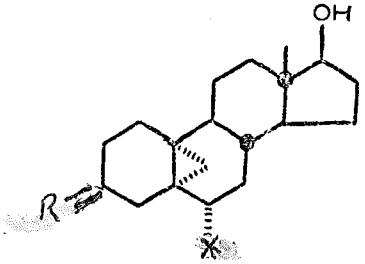


(17) (R = Et or Me)

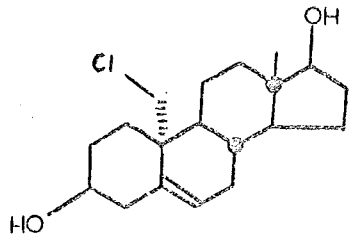


(18)

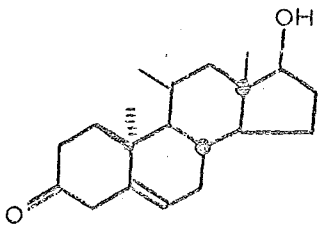


19(a) R = OTHP(β) X=OH

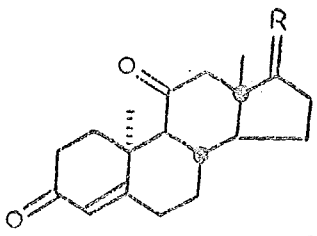
(b) R = O, X = H



(20)



(21)

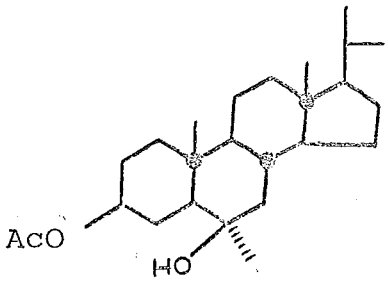


β C(6) $CH_2(OH)$.

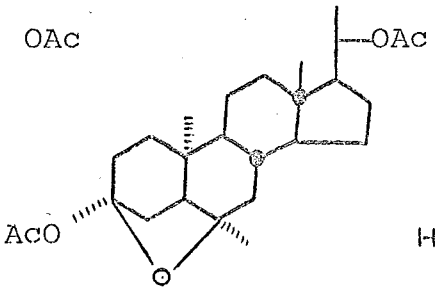
22(a) R = αOH,

(b) R = β C(6) CH_3, α H

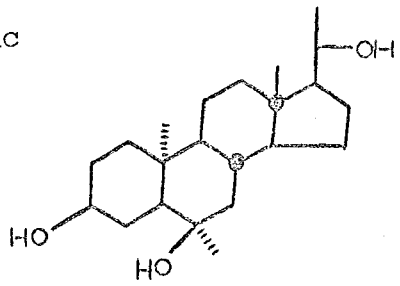
(c) R = O



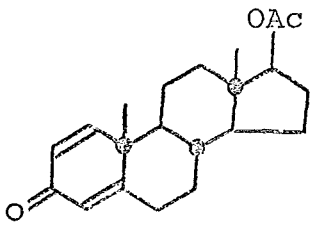
(23)



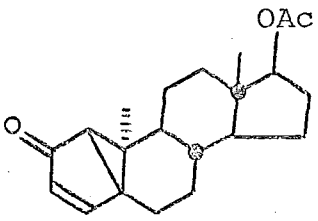
(24)



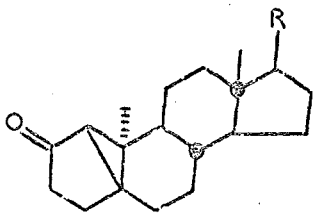
25



(26)

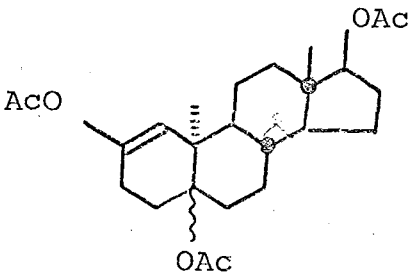


(27)

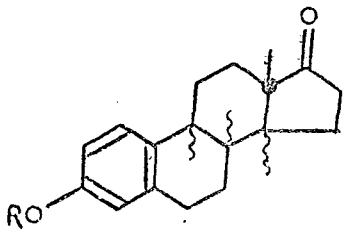


28(a) R = OAc

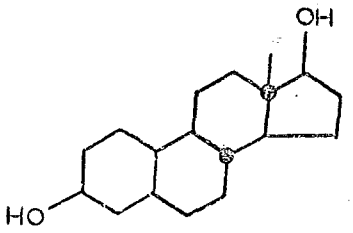
(b) R = C_8H_{17}.



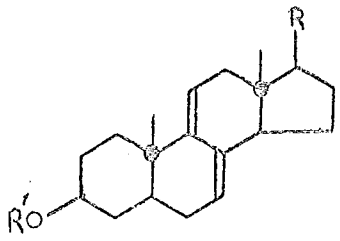
(29)



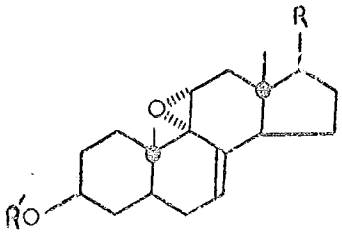
	R	C(14)	C(8)	C(9)
30(a)	Me	α	β	β
(b)	Me	α	β	β
(c)	Me	α	β	α
(d)	Me	α	α	α
(e)	H	α	α	α



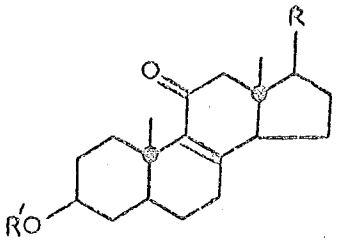
(31)



(32)

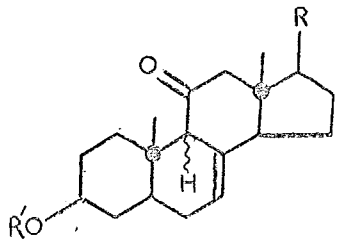


(33)

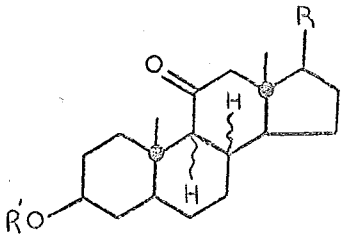


(34)

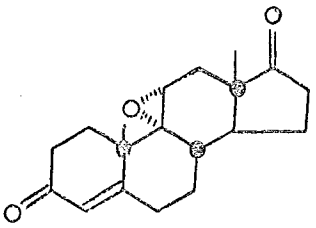
(32)-(36) R = C_8H_{17}, C_9H_{17} or H; R' = OAc



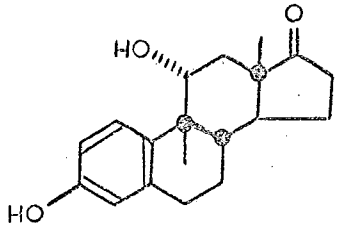
35(a) 9β
35(b) 9α



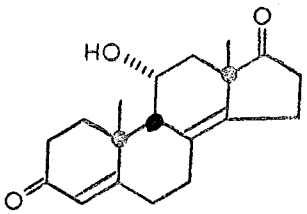
36(a) 8β9β
36(b) 8β9α



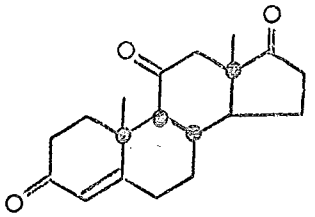
(37)



(38)



(39)



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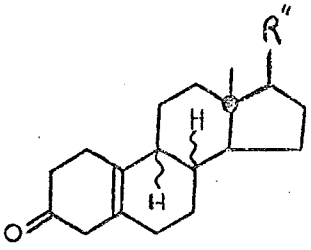
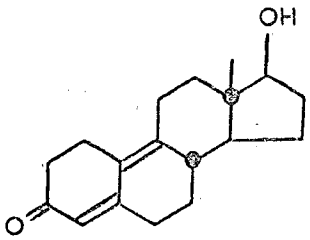
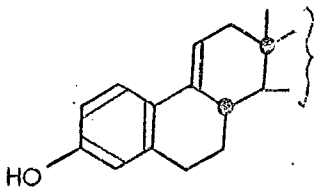


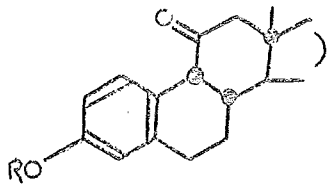
	R''	C(8)	C(9)
41(a)	0	β	β
41(b)	0	α	α
41(c)	βOH	α	α



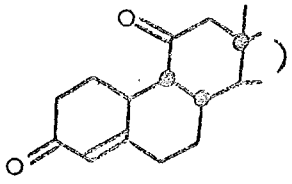
(42)



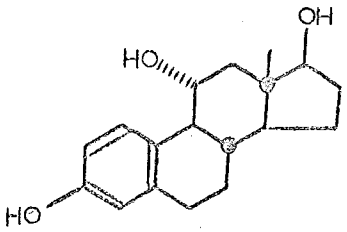
(43)



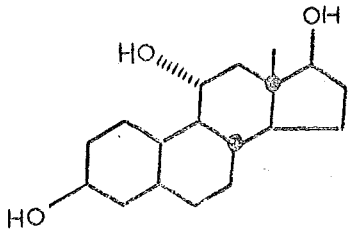
44 (a) R=H
44 (b) R=Me



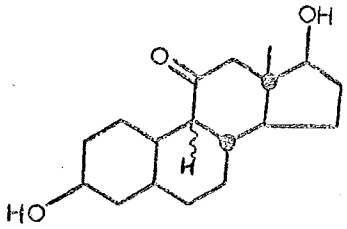
(45)



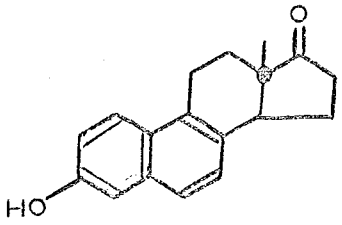
(46)



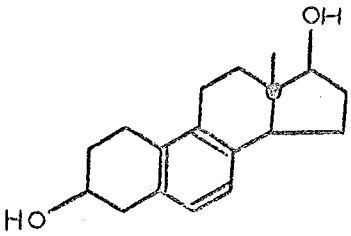
(47)



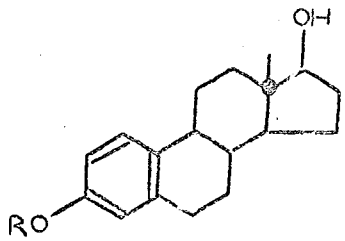
48 (a) 9α
48 (b) 9β



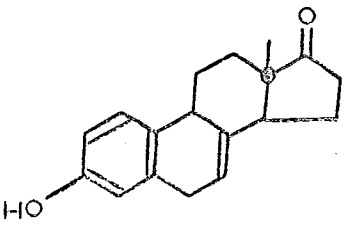
(49)



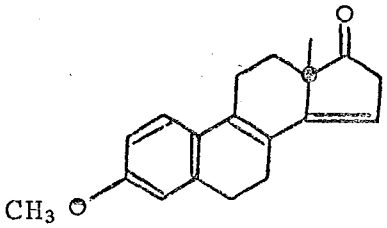
(50)



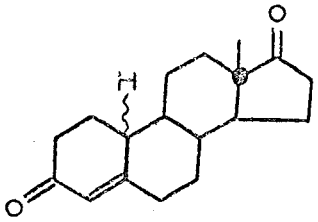
51 (a) R=H
51 (b) R=Me



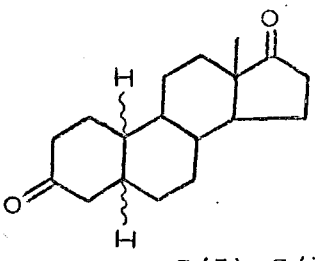
(52)



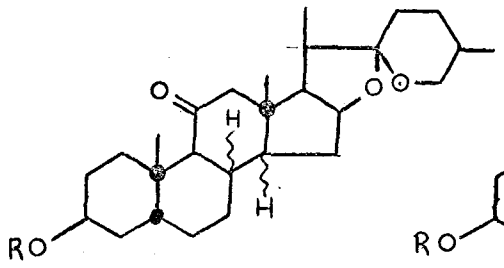
(53)



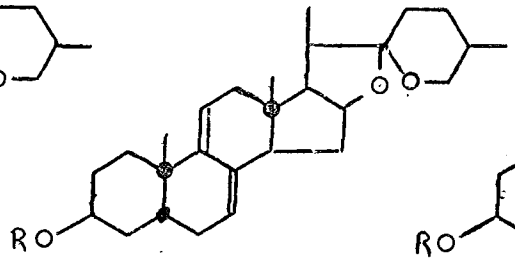
54 (a) 10α
54 (b) 10β



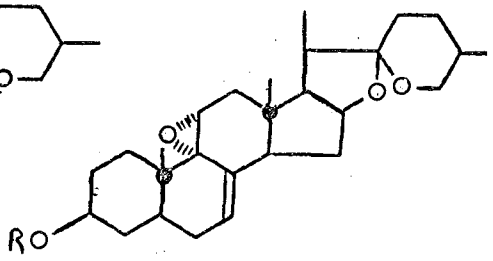
	C(5)	C(10)
55 (a)	α	α
55 (b)	β	β
55 (c)	α	β
55 (d)	β	α



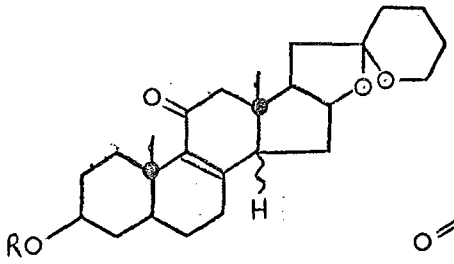
(56)



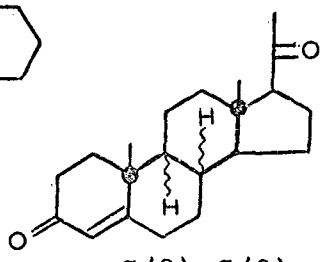
(57)



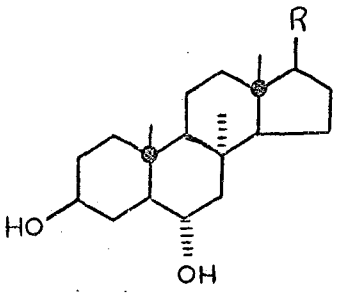
(58)



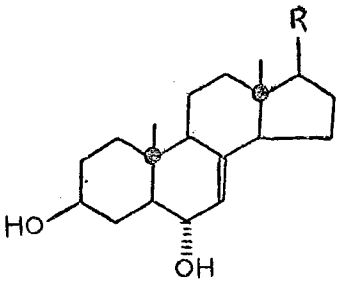
59(a) 14α
59(b) 14β



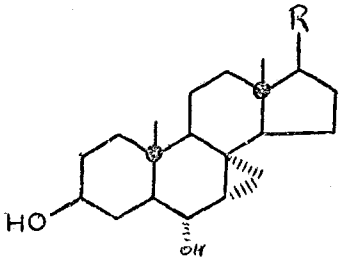
	C(8)	C(9)
60(a)	α	α
60(b)	β	β



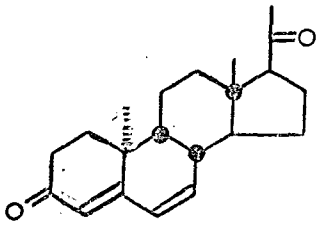
61(a) R = OAc
61(b) R = C_8H_{17}



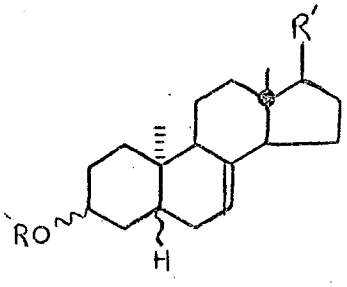
62(a) R = OAc
62(b) R = C_8H_{17}



63(a) R = OAc
63(b) R = C_8H_{17}

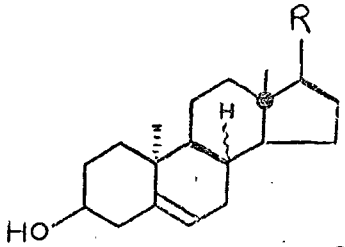


(64)

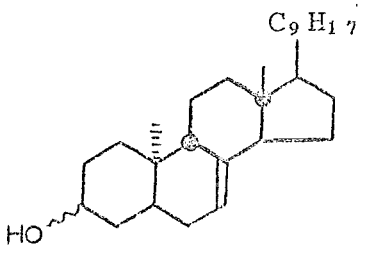


(65)

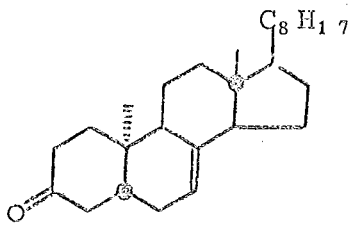
	R	R'	C(3)	C(5)
65(a)	H	C_9H_{17}	β	β
65(b)	H	C_9H_{17}	β	α
65(c)	H	C_8H_{17}	β	β
65(d)	H	C_8H_{17}	β	α
65(e)	H	C_9H_{17}	α	α
65(f)	Ac	C_8H_{17}	β	β



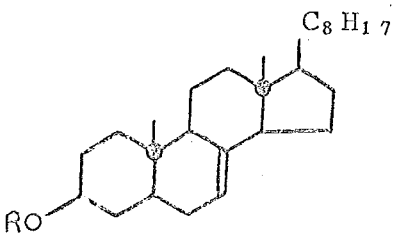
66(a) R=C_9H_{17} 8β
66(b) R=C_8H_{17} 8β
66(c) R=C_8H_{17} 8α



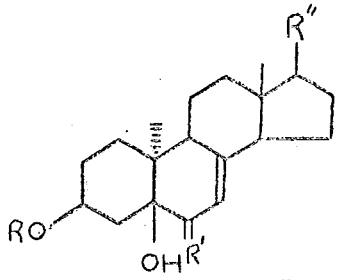
67(a) 3α
67(b) 3β



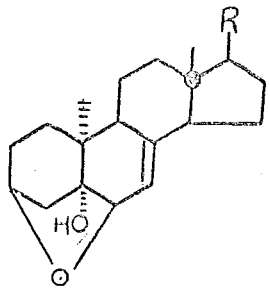
(68)



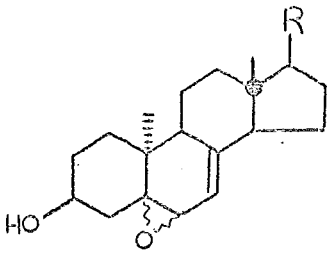
69(a) R = H
69(b) R = Ac



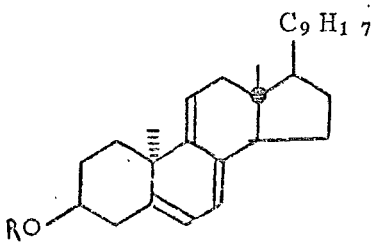
	R	R'	R''
70(a)	H	βOBz	C_9H_{17}
70(b)	H	αOBz	
70(c)	H	αOH	
70(d)	H	αOH	C_8H_{17}
70(e)	Ac	αOAc	
70(f)	H	O	
70(g)	H	αOAc	
70(h)	H	βOH	
70(i)	Ac	O	



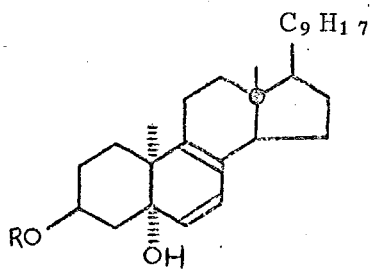
71(a) R = C_9H_{17}
71(b) R = C_8H_{17}



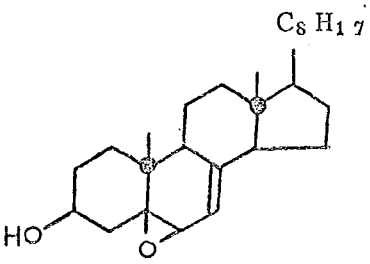
	R	C(5),C(6)
72(a)	C_9H_{17}	ββ
72(b)	〃	αα
72(c)	C_8H_{17}	ββ
72(d)	〃	αα



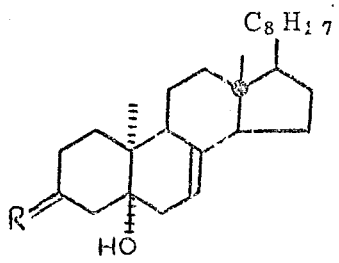
(73) (R=Ac)



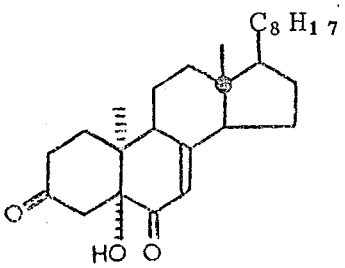
(74) (R=Ac)



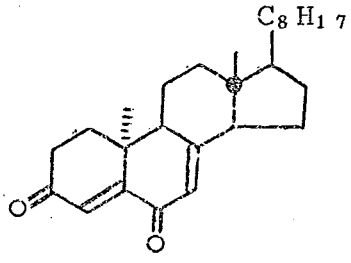
(75)



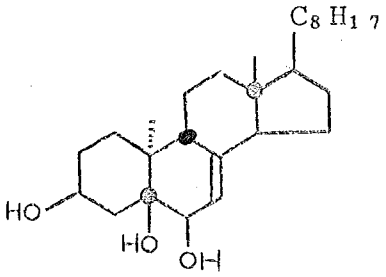
76(a) R = βOH
(b) R = O



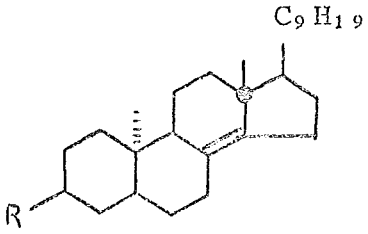
(77)



(78)

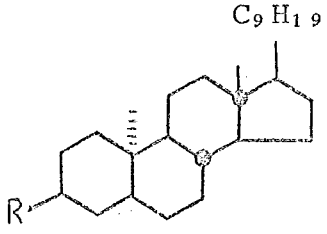


(79)



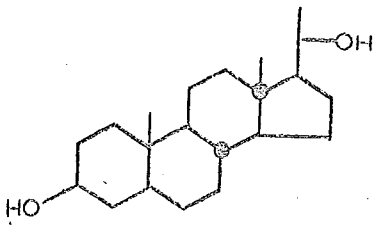
80(a) R=OAc

80(b) R=H

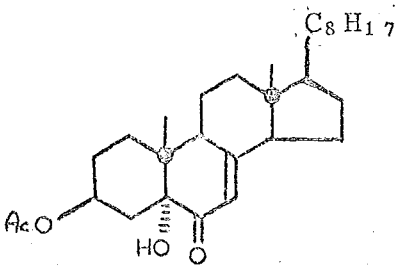


81(a) R=OAc

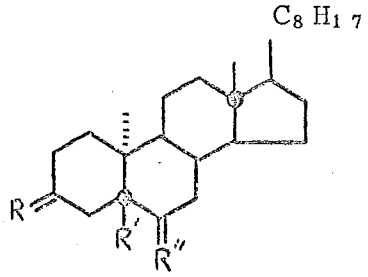
81(b) R=H



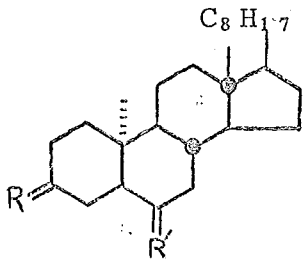
(82)



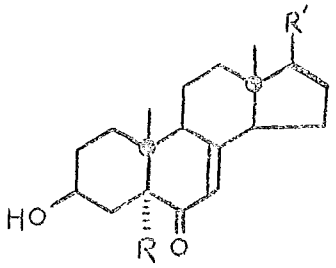
(83)



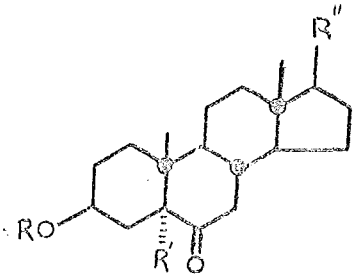
	R	R'	R''
84(a)	βOH	H	O
84(b)	βOH	OH	O
84(c)	βOH	OH	αOH
84(d)	βOH	OH	βOH
84(e)	βOH	H	βOH
84(f)	βOAc	H	O
84(g)	O	H	O
84(h)	βOAc	H	αOAc
84(i)	βOH	H	αOH
84(j)	βOAc	OH	O
84(k)	βOAc	OH	αOAc
84(l)	O	OH	O
84(m)	βOAc	H	βOAc
84(n)	βOH	H	βOAc
84(o)	O	H	βOAc



	R	R'
85(a)	βOH	αOH
85(b)	βOH	O
85(c)	βOH	βOH
85(d)	βOH	O
85(e)	βOH	αOAc
85(f)	βOAc	αOAc
85(g)	O	αOAc
85(h)	O	O
85(i)	βOH	βOH

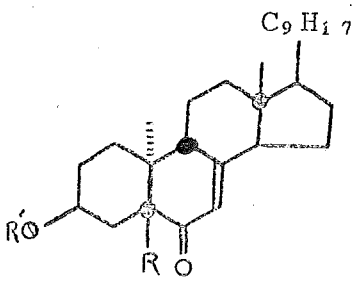


	R	R'
86 (a)	OH	C_8H_{17}
86 (b)	OH	C_9H_{17}
86 (c)	H	C_8H_{17}
86 (d)	H	C_9H_{17}



87 (R=Ac)

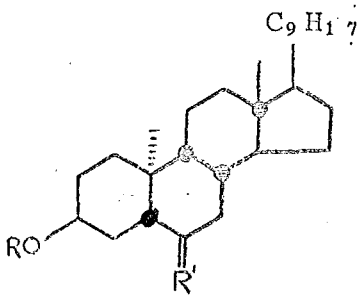
	R'	R''
(a)	OH	C_8H_{17}
(b)	OH	C_9H_{17}
(c)	H	C_8H_{17}
(d)	H	C_9H_{17}



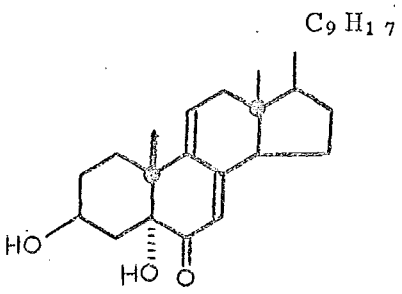
88 (R'=Ac)

(a) R=OH

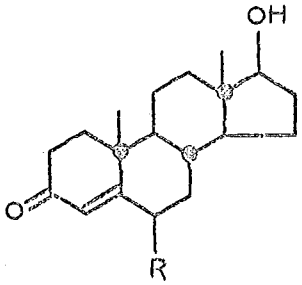
(b) R=H



	R	R'
89 (a)	Ac	O
89 (b)	Ac	βOAc
89 (c)	H	αOH

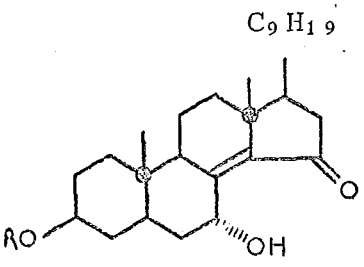


(90)

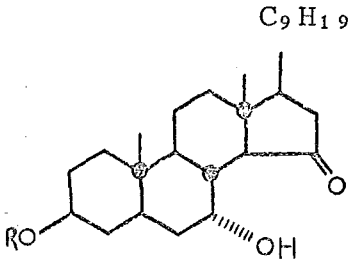


91 (a) R=OH

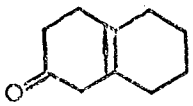
91 (b) R=H



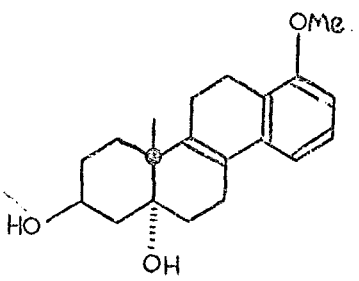
(92) R=Ac



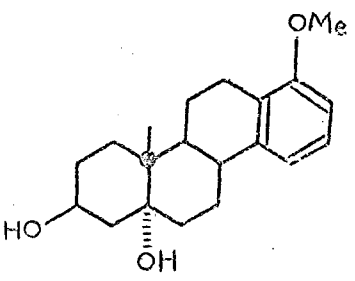
(93) R=Ac



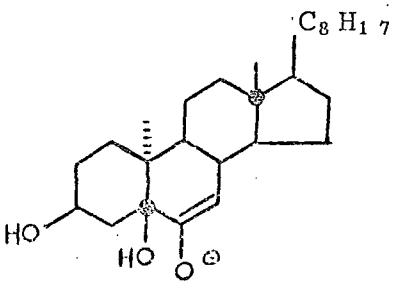
(94)



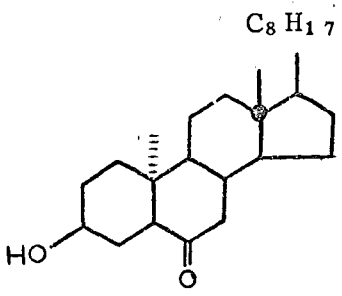
(95)



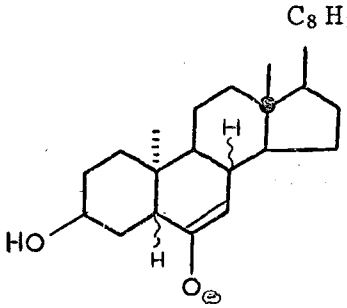
(96)



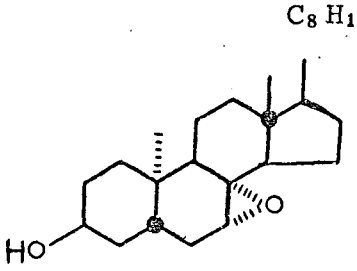
(97)



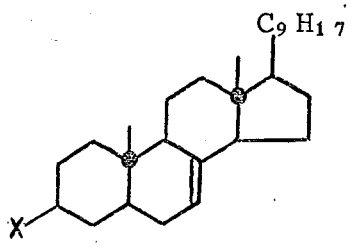
(98)



(99)

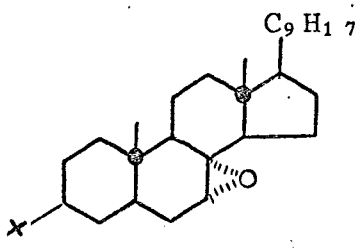


(100)

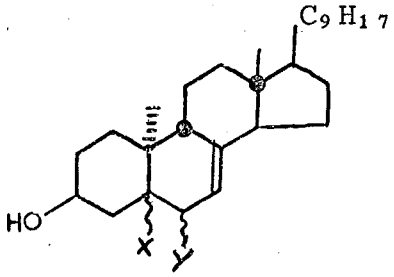


(101)

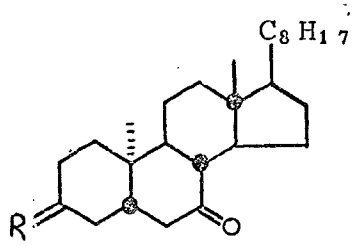
X = OH, H, OAc, OMe



(102)



(103)



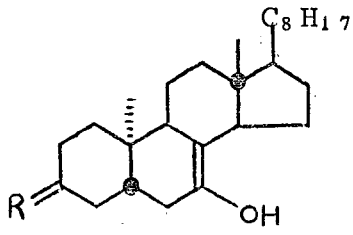
R

104(a) βOH

104(b) βOAc

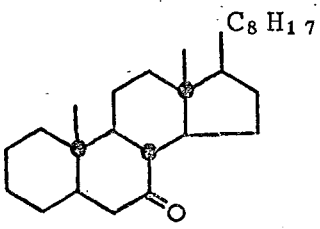
104(d) βHC(0)0-

104(c) O

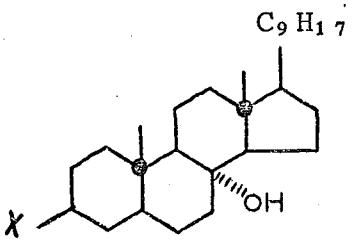


(106)

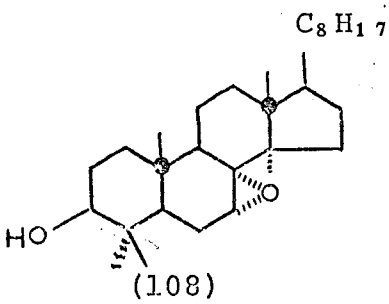
R = 0 or βOH



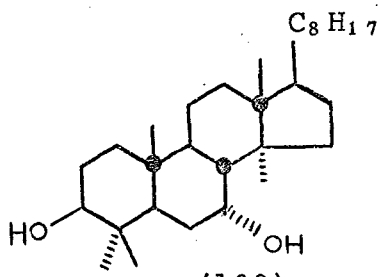
(105)



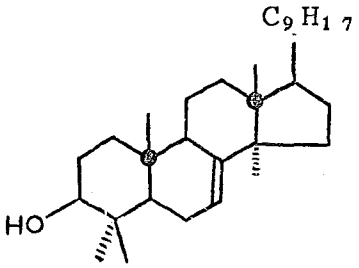
(107)



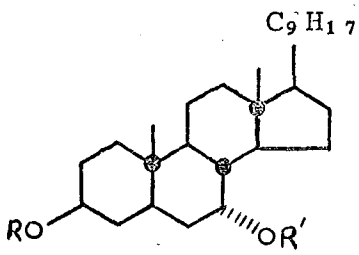
(108)



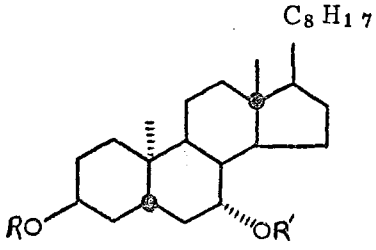
(109)



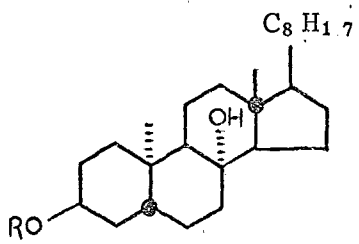
(110)



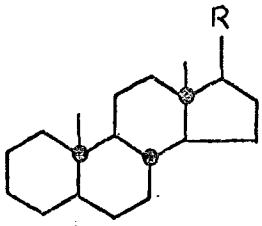
	R	R'
111(a)	H	H
111(b)	Ac	H
111(c)	Ac	Ac



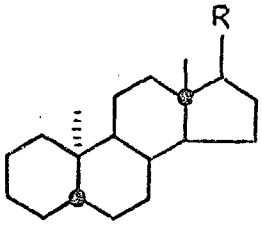
	R	R'
112(a)	Ac	Ac
112(b)	H	H



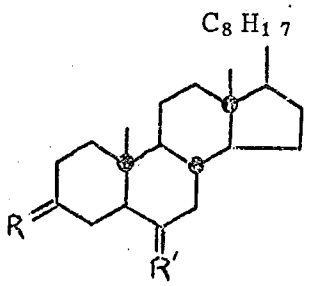
113(a) R=Ac
113(b) R=H



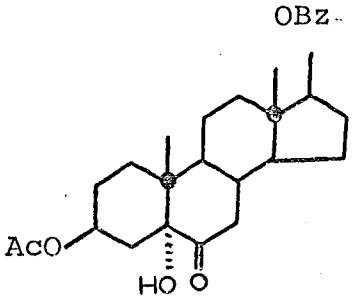
114(a) R=H
114(b) R=C8H17



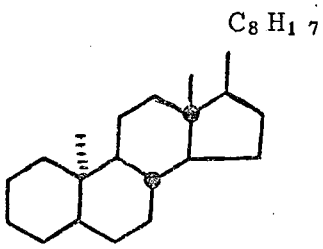
115(a) R=C8H17
115(b) R=C2H5
115(c) R=H



	R	R'
116(a)	αOH	αOH
116(b)	αOH	αOAc
116(c)	αOAc	αOAc
116(d)	αOH	O
116(e)	αOH	βOH
116(f)	O	O
116(g)	αOAc	βOAc
116(h)	αOAc	O
116(i)	O	αOAc



(117)



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